THE MEDICAL CLINICS OF NORTH AMERICA

SEPTEMBER 1979

APPLIED NUTRITION
IN CLINICAL MEDICINE

CORNELL UNIVERSITY
MEDICAL COLLEGE
LIBRARY

Digitized by the Internet Archive
in 2023 with funding from
Kahle/Austin Foundation

https://archive.org/details/medicalclinicsof0063unse

THE MEDICAL CLINICS OF NORTH AMERICA

VOLUME 63 / NUMBER 5
SEPTEMBER 1979

SYMPOSIUM ON
APPLIED NUTRITION IN CLINICAL MEDICINE

Sheldon Margen, M.D., and
Bette Caan, M.S., *Guest Editors*

W. B. SAUNDERS COMPANY — Philadelphia · London · Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Library of Congress Cataloging in Publication Data
Main entry under title:

Symposium on applied nutrition in clinical medicine.

(The Medical clinics of North America; v. 63, no. 5)
1. Diet therapy. 2. Nutrition. I. Margen, Sheldon. II. Caan, Bette.
III. Series: Medical clinics of North America; v. 63, no. 5. [DNLM:
1. Diet therapy. 2. Nutrition. W1 ME252R v. 63 no. 5 / WB400.3 S987]
RC60.M4 vol. 63, no. 5 [RM216] 616'.008s [615'.854]
79-16629

The Medical Clinics are also published in other languages, by the following:

Spanish	Nueva Editorial Interamericana, S. A. de C. V., Cedro 512, Apartado 26370, Mexico 4, D.F., Mexico
Italian	Piccin Editore, Via Porciglia, 10, 35100 Padua, Italy
Greek	Anglo-Hellenic Agency, 5 Koumpari Street, Athens 138, Greece
Portuguese	Editora Interamericana do Brazil Ltds., Av. Venezuela 131 2. Andar, Rio de Janeiro
Turkish	Guven Bookstore, Mudafaa Cad. 16-B, P.O. Box 145, Kizilay, Ankara

THE MEDICAL CLINICS OF NORTH AMERICA
September 1979 Volume 63—Number 5

© 1979 by W. B. Saunders Company. Copyright under the International Copyright Union. All rights reserved. This publication is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Made in the United States of America.

The Medical Clinics of North America (USPS 337-340) is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08002. Subscription price is $27.00 per year. Second class postage paid at Cherry Hill, New Jersey 08002. POSTMASTER: Send address changes to W. B. Saunders Co., West Washington Square, Phila., PA 19105.

This issue is Volume 63, Number 5.

The editor of this publication is Doris J. Holmes, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 17-28505.

Contributors

GEORGE L. BLACKBURN, M.D., Ph.D., Associate Professor of Surgery, Harvard Medical School; Director, Nutrition Support Service, New England Deaconess Hospital, Boston, Massachusetts

ROBERT E. BURCH, M.D., Chief, Medical Service, Huntington VA Medical Center; Professor and Associate Chairman, Department of Medicine, Marshall University School of Medicine, Huntington, West Virginia

BETTE CAAN, M.S., Nutrition Consultant, Berkeley, California

ANN M. COULSTON, M.S., R.D., Research Dietitian, General Clinical Research Center, Stanford University School of Medicine, Stanford, California

JOSEF E. FISCHER, M.D., Christian R. Holmes Professor and Director, Department of Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio

RONALD S. GOOR, Ph.D., Coordinator, Lipid Research Clinics Coronary Primary Prevention Trial, Lipid Metabolism Branch, Division of Heart and Vascular Diseases, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland

HENRY K. J. HAHN, Ph.D., Research Chemist, Huntington VA Medical Center; Assistant Professor, Department of Biochemistry, Marshall University School of Medicine, Huntington, West Virginia

MALCOLM A. HOLLIDAY, M.D., Professor of Pediatrics, and Chief, Pediatric Nephrology, University of California, San Francisco, California

DAVID HORWITZ, M.D., Assistant Professor of Medicine, University of Chicago, Chicago, Illinois

MARK A. KORSTEN, M.D., Assistant Professor of Medicine, Mount Sinai School of Medicine; Staff Physician, Veterans Administration Hospital, Bronx, New York

BERNARD LEVIN, M.D., Associate Professor of Medicine, University of Chicago, Chicago, Illinois

ROBERT I. LEVY, M.D., Director, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland

CHARLES S. LIEBER, M.D., Professor of Medicine and Pathology, Mount Sinai School of Medicine; Chief, Section of Liver Disease and Nutrition, and Director, Alcoholism Research and Treatment Center, Veterans Administration Hospital, Bronx, New York

KATHRYN McHENRY-RICHARDON, M.S., M.P.H., Nutritionist, Pediatric Nephrology, University of California, San Francisco, California

ROBERT A. MARCUS, M.D., Assistant Professor of Medicine, Stanford University School of Medicine, Stanford, California

SHELDON MARGEN, M.D., Professor, Department of Social and Administrative Health Sciences, School of Public Health, University of California, Berkeley, California

ERNEST NEWBRUN, D.M.D., Ph.D., Professor of Oral Biology, Department of Oral Medicine and Hospital Dentistry, University of California, San Francisco, California

ANTHONY A. PORTALE, M.D., Fellow, Pediatric Nephrology, University of California, San Francisco, California

GERALD M. REAVEN, M.D., Professor of Medicine, Stanford University School of Medicine, and Director, Geriatric Research, Education and Clinical Center, Veterans Administration Medical Center, Palo Alto, California

BASIL M. RIFKIND, M.D., Chief, Lipid Metabolism Branch, and Deputy Associate Director for Etiology of Arteriosclerosis, Hypertension and Lipid Metabolism, Division of Heart and Vascular Diseases, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland

DAPHNE A. ROE, M.D., Professor of Nutrition, Division of Nutritional Sciences, Cornell University; Physician, Tompkins County Hospital, Ithaca, New York

MAURICE E. SHILS, M.D., Ph.D., Associate Professor of Medicine, Cornell University Medical College; Attending Physician, Memorial Sloan-Kettering Cancer Center, New York, New York

PAUL A. THORNTON, Ph.D., Research Fellow, Harvard Medical School, on leave from Department of Clinical Nutrition, University of Kentucky Medical Center, Lexington, Kentucky

Contents

Foreword 909

Current Status of the Role of Dietary Treatment in the Prevention and Management of Coronary Heart Disease 911

Basil M. Rifkind, Ronald S. Goor, and Robert I. Levy

The relationship of plasma cholesterol to coronary heart disease is based on powerful prospective studies and supplemented by evidence from many experimental sources. The relationship of this and other risk factors to coronary disease and the current status of therapeutic and prophylactic interventions are reviewed.

Nutritional Management of Diabetes 927

Gerald M. Reaven, Ann M. Coulston, and Robert A. Marcus

A successful program of dietary intervention may provide substantial if not complete amelioration of metabolic abnormalities for the majority of diabetics. Thus physicians must take an aggressive posture toward dietary management of diabetes. Metabolic effects are discussed, and suggestions for improving patient compliance are presented.

Nutritional Management of Chronic Renal Disease 945

Malcolm A. Holliday, Kathryn McHenry-Richardson, and Anthony Portale

Nutrition therapy in renal disease is based on the concepts that (1) as renal capacity for excreting dietary excess and metabolic byproducts diminishes, dietary

intake of certain nutrients must be limited, and (2) renal failure itself may lead to deficiencies of certain nutrients. Specific recommendations for nutrients in children and adults are presented.

Nutrition in the Alcoholic **963**

Mark A. Korsten and Charles S. Lieber

Alcohol and nutrition may interact at various levels. By displacing food from the diet and suppressing appetite, alcohol often decreases the ingestion of essential nutrients. By injuring the liver, pancreas, or bowel, alcohol may compromise the digestive and absorptive functions of the gastrointestinal tract. And finally, by its obligatory breakdown to acetaldehyde in the liver, alcohol alters the metabolism and activation of other dietary constituents.

Hyperalimentation **973**

Josef E. Fischer

As widespread use of parenteral nutrition enters its second decade, a great deal of progress has been made both in safety and the development of new solutions. Current indications, complications, and new developments are discarded.

Interactions Between Drugs and Nutrients **985**

Daphne A. Roe

Nutrient and non-nutrient constituents of foods can interact with drugs to alter the predictable effect of the drug. Outcomes of drug-food, drug-alcohol, and drug-nutrient interactions include a change in the rate or level of drug absorption, change in the rate of drug metabolism, drug-food or drug-alcohol incompatibility, as well as nutritional deficiencies. Megadoses of vitamins can also alter drug responsiveness. Finally, nutrients can be used as drugs not only for deficiency diseases but also for their pharmacological effects in other disorders.

Nutritional Problems Induced by Cancer **1009**

Maurice E. Shils

Both cancer and its treatment can produce difficult nutritional problems, from the striking "cancer cachexia" and localized neoplastic effects to con-

comitants of radiation therapy and surgery. Principles of nutritional therapy in cancer patients are summarized.

Diet and Nutrition as Modifying Factors in Tumor Development 1027

Maurice E. Shils

Epidemiologic data have shown relationships between neoplastic development and dietary practices. In addition, nutrients have been shown to have roles as inhibitors and modifers of carcinogens, so there is special interest in certain dietary or nutritional factors as possible protective mechanisms. Nutrition also affects immune status, and efforts may be made to improve immunity either by improving nutritional status or, alternatively, by inducing certain deficiencies in an effort to slow tumor growth and enhance immune responses.

Dietary Fiber 1043

Bernard Levin and David Horwitz

Epidemiologic data suggesting that increased fiber intake may prevent or treat a wide variety of ailments suffer in that comparisons of highly diverse populations make it difficult to identify and isolate causal differences from those of no consequence. To evaluate critically the evidence for possible preventive or therapeutic effects, it is necessary to consider current concepts of the physicochemical nature of fiber and the complex modes by which fiber may influence gastrointestinal, endocrine, and lipid physiology.

Trace Elements in Human Nutrition 1057

Robert E. Burch and Henry K. J. Hahn

Trace element deficiencies can result from inadequate dietary intake (generalized malnutrition), impaired intestinal absorption, excessive excretion, certain disease states, as well as in patients maintained on prolonged parenteral nutrition without trace element supplements. Copper and zinc deficiencies have recently been reported with total parenteral nutrition.

Dietary Carbohydrates: Their Role in Cariogenicity 1069

Ernest Newbrun

Controlled human studies have established that the incidence and prevalence of caries can be markedly

diminished by reducing the frequency of sugar consumption, and there is increasing epidemiologic evidence that in many large populations the prevalence of caries rises and falls with changes in total sugar consumption. Dietary modification is therefore critical in any dental preventive program.

Dietary Recommendations for the Maintenance of Dental Health **1087**

Bette Caan

Dietary recommendations for oral health involve the promotion of foods that are nutritionally sound and whose consumption over long periods of time will maintain oral health as well as optimal overall health.

Evaluation of Nutritional Status in the Outpatient Setting **1095**

Sheldon Margen

As we increasingly learn the importance of nutrition as a concomitant of various illnesses and the possible contribution of malnutrition per se to chronic diseases, it becomes mandatory for the physician to incorporate a more thorough nutritional status evaluation into every physical examination, whether for a specific complaint or for routine health care.

Nutritional Assessment of the Hospitalized Patient **1103**

George L. Blackburn and Paul A. Thornton

While some symptoms of the malnourished state are obvious, others may be subtle. Careful assessment is indicated to uncover inconspicuous symptoms and to quantitate those that are apparent. Various tests for malnutrition are discussed, as well as immune system competence and nutrition/metabolism profile.

Nutrition Resources **1117**

Sarah Finkelhor

A variety of sources for nutrition education are available in the community, from federally funded programs to concerned neighborhood organizations. All may be utilized in educating patients to good nutrition.

Index **1125**

RECENT SYMPOSIA

November 1978
Renal Therapeutics

January 1979
Cardiac Emergencies

March 1979
Therapeutic Problems

May 1979
Treatment of Liver Disease

July 1979
Clinical Neurology: New Approaches to Old Problems

FORTHCOMING SYMPOSIA

November 1979
Medical Evaluation of the Preoperative Patient
Lourdes C. Corman, M.D., and
Robert J. Bolt, M.D., *Guest Editors*

January 1980
Noninvasive Cardiac Diagnosis I
Irwin R. Callen, M.D., *Guest Editor*

March 1980
Noninvasive Cardiac Diagnosis II
Irwin R. Callen, M.D., *Guest Editor*

May 1980
Infectious Lung Diseases
Jerome S. Putnam, M.D., and
Carmelita U. Tuazon, M.D., *Guest Editors*

July 1980
Hematologic Disorders
Albert F. LoBuglio, M.D., *Guest Editor*

Foreword

BETTE CAAN, M.S. SHELDON MARGEN, M.D.

It is interesting to take a brief historical look at how a volume on clinical nutrition came to merit publication. Early scientific medicine and nutrition really developed hand in hand. In fact, one might say that the scientific revolution, the early discoveries of chemistry and later biochemistry, were closely related to nutrition. However scientific medicine, particularly in the delivery of services and the diagnoses and treatment of illness, began to make rapid advances without recognizing the role of nutrition in health and disease. The science of nutrition was confined primarily to the identification and functions of vitamins.

As each of the vitamins was identified, the peril of deficiency diseases was removed. By the early 1930's most of the nutrients had supposedly been discovered, and most deficiency diseases were fairly well eliminated, or at least the potential for their elimination was known. With the supposed completion of the discovery of vitamins the field was considered virtually closed. The assumption was made that the medical profession had little to gain by devoting time to learning the area of nutrition. Nutrition became identified with "dietetics," where a prescription was given to modify food intake for very specific diseases, and very few advances were made in nutritional research. It has only been over the last 25 years, based on scientific laboratory studies and extensive epidemiologic evidence, that we recognize that nutrition may play an important role in the quality of life as well as in the prevention and treatment of many diseases.

Because nutrition is a broad, interdisciplinary field it is extremely complex both to teach and to practice, and only recently have physicians developed an interest in the clinical application of nutritional principles.

It has therefore been the desire of the editors to point out some of the important and frequently controversial areas where nutrition may play a significant role in the prevention, treatment and or amelioration of disease. This volume is aimed at the clinical practitioner, particularly the internist and generalist, to serve as an orientation to some of the current

problems of clinical malnutrition. Most of these papers have been written by eminent authorities in their field, and reflect the forefront of nutritional research which is valuable to the clinician. Lacking specific training in nutrition, few physicians can truly call themselves clinical nutritionists. However, as with other interdisciplinary areas of medicine, there is a pool of well trained professional nutritionists who can work with physicians, and we believe that this is the road to the future. Nevertheless, the physician must still have a thorough knowledge and awareness of potential nutritional problems so that malnutrition can be recognized, and the measures necessary for its correction instituted. We hope this issue will be of use to practicing clinicians and will broaden their perspectives on the wide variety of areas which it opens.

BETTE CAAN, M.S.
SHELDON MARGEN, M.D.
Guest Editors

Nutritional Science Department
119 Morgan Hall
University of California
Berkeley, California 94704

Current Status of the Role of Dietary Treatment in the Prevention and Management of Coronary Heart Disease

Basil M. Rifkind, M.D., Ronald S. Goor, Ph.D.,** and Robert I. Levy, M.D.****

Coronary heart disease is the leading cause of death in the United States. Although its incidence has been dropping recently, it is still responsible for close to 750,000 deaths per year.[1] Twice as many people die from coronary heart disease as from *all* cancers (the second major cause of death). Moreover, as the major cause of premature death in males, coronary heart disease is the reason that life expectancy for women is about 10 years longer than for men.

Clinical manifestations of coronary heart disease develop in about 20 per cent of men under the age of 60. A quarter of them die within three hours of the first symptoms. Many never reach a hospital. Another quarter die in the first few weeks after a heart attack. Advances in intensive in hospital care are not likely to reduce mortality from sudden death and can only partially impact the death rates in hospitals and during post-event rehabilitation.

The prevalence of coronary heart disease in the United States is ten times that in Japan, which enjoys the lowest rates in the modern industrialized world. If we wish to approach such low rates, with the concomitant increase in life span, especially for men, we must think in terms of preventing rather than curing the underlying disease. Coronary heart disease is caused primarily by atherosclerosis of the coronary arteries. Since this process results in a chronic progressive hardening of the arteries which begins in childhood and is already quite

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

*Chief, Lipid Metabolism Branch, and Deputy Associate Director for Etiology of Arteriosclerosis, Hypertension and Lipid Metabolism, Division of Heart and Vascular Diseases

**Coordinator, Lipid Research Clinics Coronary Primary Prevention Trial, Lipid Metabolism Branch, Division of Heart and Vascular Diseases

***Director, National Heart, Lung, and Blood Institute

advanced by early adulthood, preventive measures will probably be most effective if applied over the entire life span. Who then is at risk and how are these individuals identified?

RISK FACTORS FOR CORONARY HEART DISEASE

Although case-control studies are valuable in identifying possible risk factors for coronary heart disease, they are subject to the potential fallacy that the abnormal level of a given measurement, such as cholesterol, in subjects with coronary heart disease may result from rather than precede the onset of the coronary heart disease. Prospective studies, especially those in which the baseline observations long antedate the clinical manifestations of disease, are free of this potential bias. Numerous prospective studies, both in the United States and abroad, have identified three major risk factors for coronary heart disease, namely: the total plasma cholesterol level, the systolic and diastolic blood pressure, and the number of cigarettes one smokes; the higher the level of any one of these, the greater the risk for coronary heart disease.[31] Recently the use of plasma total cholesterol has been further defined with the observation that while the level of low-density lipoprotein (LDL)—the major cholesterol carrier in the blood—is strongly and directly related to coronary heart disease, the level of high-density lipoprotein (HDL) is inversely related to risk of coronary heart disease.[18] The lower the high-density lipoprotein, the greater the risk for coronary heart disease. The aforementioned prospective studies in the United States have shown good general agreement in their estimates of risk associated with these various factors. Their predictive power has also been put to the test and has been validated.

Our primary interest here is in cholesterol as a risk factor. It should be noted that coronary heart disease is directly related to cholesterol values across the range encountered in the United States populations; that is, there is no cholesterol level below which coronary disappears. As discussed later, this has implications as to who should be considered for reduction in cholesterol level by dietary means.

Plasma Cholesterol and Coronary Heart Disease

The relationship of plasma cholesterol to coronary heart disease, however, is not based solely on the evidence from the powerful prospective studies; it is supplemented by evidence from many experimental sources.

1. Cholesterol is an important component of the atherosclerotic plaque.

2. Diet-induced hypercholesterolemia in many experimental animals, including the non-human primate, leads to atherosclerosis. Regression of diet-induced atherosclerosis may be obtained by lowering plasma cholesterol either by reinstituting a normal diet or by use of cholesterol-lowering biliary sequestrants.

3. Various genetic forms of hypercholesterolemia, for example, fa-

milial hypercholesterolemia, are associated with premature coronary heart disease. The homozygous form of familial hypercholesterolemia is especially striking in this respect, with coronary disease usually appearing within the first or second decades, and leading to an early death.

4. International comparisons show that plasma cholesterol levels generally correlate with prevalence of coronary heart disease and the severity of atheroslcerosis.

5. Metabolic studies are gradually defining the ability of lipoproteins to transport cholesterol to and from the arterial wall. They show that essentially all the cholesterol in atherosclerotic plaques is derived from that circulating in the blood.

It should also be emphasized that although there is unquestionable evidence for a relationship between cholesterol and coronary heart disease, this should not obscure the importance of other risk factors. Also, a great deal remains to be learned about how the various risk factors interact and how raised low-density lipoprotein levels and decreased high-density lipoprotein levels relate to coronary heart disease (about 70 per cent of the plasma cholesterol is normally carried by the atherogenic low-density lipoprotein; about 20 per cent of the plasma cholesterol is carried by the protective high-density lipoprotein).

Triglycerides and Coronary Heart Disease

Following observations that plasma triglyceride levels tended to be higher in subjects with coronary heart disease than in controls, several prospective studies evaluated the risk factor status of triglyceride.[16] In the fasting subject, free of chylomicrons, triglyceride is carried mainly in the very-low-density lipoprotein (VLDL) fraction. Many studies have found that plasma triglyceride is directly related to the risk of subsequent development of coronary heart disease. However, almost all these studies have found that, when the relationship of triglyceride to other risk factors (such as plasma cholesterol, obesity, sedentary lifestyle, hypertension, or impaired glucose tolerance) is taken into account, then triglyceride (and VLDL) is not independently correlated with risk for coronary heart disease. (An exception to this may occur in women over 50.)

DIET AND PLASMA CHOLESTEROL

The importance of plasma cholesterol levels in the development of coronary heart disease has led, in turn, to a search for the factors that determine plasma cholesterol levels in populations and in individuals. Dietary factors have long been suspected to play a major role. Among the earliest observations in atherosclerosis research was the production of hypercholesterolemia (and atherosclerosis) through high-fat diets, a model that has been extensively utilized in rabbits, dogs, swine and pigeons and later extended to the non-human primate.

These experiments in rabbits and other species were subsequently supplemented by reports that international differences in atherosclerosis prevalence might be explicable on the basis of dietary differences. Many investigators noted that populations with little atherosclerosis tended to consume diets high in vegetables, and populations with an increased prevalence of atheroslcerosis and its clinical sequelae consumed a fat-rich diet, high in dairy products, meat, and eggs.

International Studies

These general observations were subsequently confirmed by a host of systematic epidemiologic studies. In his recent summary of international studies of such relationships, Stamler classified them into four types.[34]

I. Analysis of Data on Nutrition and Mortality Patterns Among Nations. These analyses are generally based on Food and Agricultural Organization (FAO) and World Health Organization (WHO) data. They have consistently demonstrated a relationship between the intake of saturated fat and cholesterol, and mortality from coronary heart disease. Intakes of total calories and nutrients other than fats, such as protein and sucrose, are also correlated with prevalence of coronary heart disease,[34] and since intakes of different nutrients are highly intercorrelated, it is not possible to incriminate fats per se. However, as Stamler points out, the data do not negate the importance of fat intake, and they should be considered along with all the other evidence relating dietary fat to plasma cholesterol and coronary heart disease.

II. Analysis of Autopsy Findings from Different Countries. The pattern of investigation has been initial observation by pathologists that individuals from countries with infrequent occurrence of severe coronary atherosclerosis had low dietary fat intakes, followed by large-scale systematic studies, such as the International Atherosclerosis Project,[27] which confirmed these observations.

III. Field Investigations of Population Samples in Different Countries. Investigators have evaluated the diet, cholesterol levels, and experience with coronary heart disease in different countries and populations, using direct measurements of dietary intake, blood cholesterol, and coronary heart disease status rather than relying on indirect data for cardiovascular mortality, dietary intake or blood cholesterol. The Seven Country Study is the best known and most ambitious of these studies.[20] Based on prospective observations in 18 populations in seven countries with markedly different prevalences of coronary heart disease, it showed a high correlation among saturated fat intake, serum cholesterol levels, and prevalence of coronary heart disease.

IV. International Studies on the Effects of Migration. Movements of members of population groups from less affluent to more affluent societies provide a special opportunity to evaluate changes in risk factors. Such observations have largely been responsible for dispelling the view that atherosclerosis and coronary

heart disease essentially represent an inevitable aging process, or that the cholesterol levels encountered in most members of countries such as the United States can be regarded as normal.

Whether the population study consisted of Yemenite Jews who migrated to Israel, Japanese who migrated to Hawaii or the United States,[19] or Italian or Irish who also migrated to the United States, the results point to a consistent theme: As groups move from areas with a low incidence of coronary heart disease to areas of high incidence, they show a rise in serum cholesterol and a rise in dietary fat intake. Of course, many other dietary and lifestyle changes also occur in such groups, but again the data are consistent with a relationship among dietary fat intake, plasma cholesterol levels, and coronary heart disease.

Studies Within Population Groups

Diverse studies of dietary fat–blood fat relationships have been conducted within the United States. In some, lower cholesterol levels have been found in various types of vegetarians than in their meat-eating counterparts.[30] However, studies within single populations (for example, the Framingham Study[11]), which have attempted to correlate cholesterol levels and dietary fat intake in individuals, have failed to report a consistent and significant relationship. Opponents of a dietary fat-blood cholesterol relationship have often seized upon these results as important negative evidence (discounting the large body of diverse evidence in favor of such a relationship). It has been suggested, however, that well-known weaknesses in the methodology for measuring the dietary intake of individuals that fail to deal with large intra-individual variation in the intake of certain nutrients, especially fat, seen within the United States population, may obscure such a relationship.[26] Recently, within-group observations in both Puerto Rico and Hawaii have indeed shown a relationship between dietary fat, starch, and coronary heart disease.[13, 15]

Dietary Intervention Studies

The mass of observational data just summarized is supplemented by studies in which diet has been adjusted in groups of individuals. They show that plasma cholesterol levels can be readily lowered by means of reductions in dietary saturated fat and cholesterol intake; this has been achieved in both institutionalized or free-living populations, and in normal or hypercholesterolemic subjects.[2, 9]

In fact, reduction through dietary changes is now a standard therapeutic maneuver. Keys[21] and Hegsted[17] have developed equations to allow one to calculate the amount of cholesterol lowering that can be achieved if one reduces saturated fat or cholesterol intake, or increases polyunsaturated fat intake. It should be noted that removal of a given amount of saturated fat is twice as effective in reducing cholesterol as introduction of a similar amount of polyunsaturated fat.

IS LOWERING CHOLESTEROL LEVELS BENEFICIAL?

Serum cholesterol levels are directly related to coronary heart disease. It is possible to lower serum cholesterol by dietary (and by drug or surgical) means. Does such reduction reduce the risk of coronary heart disease? This is indeed a 64 billion dollar question, for that is the approximate current cost of coronary heart disease in this country. There have been numerous dietary (and drug) intervention studies of cholesterol-lowering, using both free-living and institutionalized populations, with or without established coronary heart disease.[4, 6, 7] Although many of these studies yielded suggestive evidence of benefit, none of them can be regarded as sufficiently conclusive; at the same time none has proved conclusively that risk of coronary heart disease is *not* diminished by reducing serum cholesterol. This indeterminacy can be attributed to problems in study design[6] such as:

1. Numbers of subjects studied were insufficient to yield statistically significant results.
2. The intervention was introduced too late in the life of subjects to reduce or halt damage developed over a lifetime.
3. Follow-up time was insufficient.
4. Serum cholesterol reduction was insufficient.
5. Randomization and double-blind procedures were not employed.
6. The statistical approaches taken to analyze the data were flawed.

That reduction in certain indices of coronary risk appeared to occur in many of the studies, even under adverse design conditions, might be an indication of the preventive potential of serum cholesterol reduction.

The most recently reported intervention study is the World Health Organization Clofibrate Trial,[4] a primary prevention trial of cholesterol-lowering in subjects with cholesterol levels within the top third of the cholesterol distribution. This study achieved a 6 to 9 per cent fall in cholesterol level and reported a 25 per cent reduction in the rate of nonfatal myocardial infarction which was not, however, accompanied by benefits in rates of fatal myocardial infarction or angina. Unfortunately, an increased noncardiovascular mortality rate was observed in the clofibrate-treated group, together with signs of systemic toxicity. The WHO study was an ambitious one which employed many satisfactory design features such as large numbers, adequate period of follow-up, the use of the double-blind, and randomization. However, its follow-up procedures can be criticized, especially with respect to nonfatal coronary events. It is also unfortunate that clofibrate has been shown to be associated with an increasing number of effects on organ function separate and distinct from its cholesterol-lowering properties. Thus, despite the encouraging results with respect to nonfatal myocardial infarction, the findings from the WHO study cannot be held to be sufficiently conclusive.

In summary, the benefit of cholesterol lowering has not yet been conclusively proven in man. Benefit remains, however, strongly presumptive based on epidemiologic studies.

OTHER DIETARY ELEMENTS AND RISK OF CORONARY HEART DISEASE

In addition to the evidence relating coronary heart disease to dietary cholesterol and fat intake, other dietary factors have been incriminated.

Obesity. Obesity has long been suspect as an important risk factor for coronary heart disease. Surprisingly, prospective studies have generally not identified obesity as an important independent risk factor, although weight gain rather than absolute weight may be more important.[1] Overweight is related to several other coronary risk factors, such as low levels of high density lipoprotein (HDL), high triglyceride levels, hyperglycemia, and hypertension. Control of obesity is an essential and often satisfactory mode of reducing elevated levels of very low density lipoprotein. Weight loss has also been claimed to reduce low-density lipoprotein (LDL) levels. In view of these various interrelationships and other noncardiovascular consequences of obesity, it is wise to have subjects strive to achieve ideal weight.

Fiber. Western diets tend to be low in fiber and it has been suggested that a low-fiber diet may be a factor in atherogenesis,[32, 38] possibly by permitting increased cholesterol absorption. Dietary fiber is a complex chemical mixture requiring better definition than at present. Many studies have failed to distinguish different types of fiber. At the present time, the evidence for fiber as a significant dietary component for coronary heart disease is scanty. It would seem prudent, however, to maintain a reasonable level of fiber in the diet, at least for proper bowel function.

Dietary Carbohydrate. International studies suggest that populations with low mortality from coronary heart disease derive a high proportion of their calories from carbohydrate, especially complex carbohydrates such as starch.[25] A high sucrose intake has been claimed to play a causal role in coronary heart disease.[37] However, the epidemiologic data, in contrast to those for dietary fat and cholesterol, are not supplemented by a large body of additional evidence relating dietary carbohydrate components to atherogenesis and coronary heart disease.[25]

Alcohol. A few recent studies have associated modest alcohol drinking with less risk for coronary heart disease.[3] Of special interest is the recent observation that such an alcohol intake, while also increasing levels of VLDL may promote increased of levels of HDL.[3] However, excessive alcohol intake can produce cardiomyopathy and is associated with much morbidity and an overall excess mortality, so that the newer observations must be treated with caution.

Trace Elements.[33] Several epidemiologic studies have suggested that soft water is associated with increased coronary heart disease. The reason for this relationship remains unclear. An increased incidence of sudden death in areas utilizing soft water points to arrhythmia rather than atherogenesis as a problem. Much more information is needed on this interesting area before any recommendations can be made.

Coffee Intake.[33] A positive correlation between CHD and coffee drinking has been reported in some studies. However, when the association between coffee drinking and cigarette smoking is taken into account, little or no independent relationship remains between coffee drinking and heart attacks.

DIETARY INTERVENTION

Two groups may be considered for dietary intervention designed to lower plasma cholesterol levels: (1) the frankly hyperlipidemic subjects at high risk for coronary heart disease and other sequelae and, (2) the North American population as a whole.

Dietary Treatment of Hyperlipidemia (Table 1)

Hyperlipidemia is said to be present when an individual's plasma cholesterol and/or triglyceride levels exceed the 95th percentile of his or her respective age and sex distributions.[24] Such definitions are continuous, and since risk of coronary heart disease is linearly related to cholesterol levels, no cutpoint separates subjects at risk from subjects free from risk. However, the definition of some subjects with specific types of hyperlipidemia by use of cutpoints has the advantage of (a) focusing attention on especially high-risk subjects and (b) concentrating on certain genetic cases of hyperlipidemia, some of which individuals have had abnormally high lipid levels since birth or early life, and who are presumably at much higher risk for coronary heart disease than subjects whose high lipid levels developed later in life. Certain forms of hyperlipidemia are associated with sequelae other than coronary heart disease.

It is desirable to translate hyperlipidemia into hyperlipoproteinemia since it is as lipoproteins that the plasma lipids circulate. Five types (patterns) of hyperlipoproteinemia are generally recognized.[12] Each may be secondary to a variety of diseases, in which case the treatment is primarily directed to the underlying disease.[22] Each may also occur as a primary, often genetically determined, abnormality. It is useful to classify hyperlipoproteinemias into these different types, despite some limitations, since each primary type has characteristic genetic, biochemical, and clinical features and each has its special dietary and drug requirements. Diet is the cornerstone of the management of primary hyperlipoproteinemia. Dietary therapy should always be instituted prior to consideration of drug or other forms of treatment. Even when additional forms of treatment are required, dietary therapy should be maintained and not discarded. A variety of dietary manipulations can be used to lower raised lipid and lipoprotein levels.[11, 16] Appropriate regimens are selected from the following elements:

1. *Dietary cholesterol is restricted to reduce elevated low-density lipoprotein levels or to prevent their rise as a result of other dietary changes.* Dietary cholesterol is found exclusively in foods containing animal fat. Examples of foods especially rich in cholesterol are

Table 1. *Summary of Diets for Types I–V Hyperlipoproteinemia*

	TYPE I	TYPE IIA	TYPE IIB AND TYPE III	TYPE IV	TYPE V
Diet Prescription	Low fat 25–35 gm	Low Cholesterol polyunsaturated fat increased	Low Cholesterol Approximately: 20% cal. Pro. 40% cal. Fat 40% cal. CHO	Controlled CHO; Approximately 45% of calories; Moderately restricted cholesterol	Restricted Fat 30% of calories; Controlled CHO 50% of calories; Moderately restricted cholesterol
Calories	Not restricted	Not restricted	Achieve and maintain "ideal" weight, i.e., reduction diet if necessary	Achieve and maintain "ideal" weight, i.e., reduction diet if necessary	Achieve and maintain "ideal" weight, i.e. reduction diet if necessary
Protein	Total protein intake is not limited	Total protein intake is not limited	High protein	Not limited other than control of patient's weight	High protein
Fat	Restricted to 25–35 gm. Kind of fat not important	Saturated fat intake limited. Polyunsaturated fat intake increased	Controlled to 40% calories (polyunsaturated fats recommended in preference to saturated fats)	Not limited other than control of patient's weight (polyunsaturated fats recommended in preference to saturated fats)	Restricted to 30% of calories (polyunsaturated fats recommended in preference to saturated fats)
Cholesterol	Not restricted	As low as possible; the only source of cholesterol is the meat in the diet	Less than 300 mg – the only source of cholesterol is the meat in the diet	Moderately restricted to 300–500 mg.	Moderately restricted to 300–500 mg.
Carbohydrate	Not limited	Not limited	Controlled – concentrated sweets are restricted	Controlled – concentrated sweets are restricted	Controlled – concentrated sweets are restricted
Alcohol	Not recommended	May be used with discretion	Limited to 2 servings (substituted for carbohydrate)	Limited to 2 servings (substituted for carbohydrate)	Not recommended

From Fredrickson, D. S., Levy, R. I., Bonnell, M., et al.: *Dietary Management of Hyperlipoproteinemia.* A Handbook for Physicians and Dietitians. Washington, D.C., U.S. Department of Health, Education, and Welfare. Publication No. (NIH)75-110, 1974.

egg yolks, dairy products (cheese, whole milk), and organ meats (liver, kidney).

2. *Saturated fat intake is reduced and some is replaced by polyunsaturated fat.* The P : S ratio of the diet is raised from about 0.3 to 2.0. These changes also lower LDL levels, possibly by increasing LDL catabolism. Saturated fats are usually of animal origin and polyunsaturated fats are usually of vegetable origin. However, certain vegetable fats such as palm oil and coconut oil are rich in saturates.

3. *Dietary fat is severely restricted*, irrespective of its degree of saturation, to prevent chylomicron formation.

4. *A program of weight reduction for obese subjects*, followed by a maintenance regimen providing protein, fat and carbohydrate in 20 : 40 : 40 proportions, is employed in the various endogenous hypertriglyceridemias to reduce VLDL or intermediate density lipoprotein (IDL) levels.

5. *Alcohol intake is decreased or eliminated;* this is an important and sometimes vital element for treatment and control of endogenous and exogenous hypertriglyceridemias.

Food Labeling[28]

The provision of information on the caloric and fat content of foods is useful for the subject on a lipid-lowering regimen. It also has potential usefulness as an educational tool to focus interest on nutrition-blood cholesterol-heart disease relationships. Current food labeling may sometimes mislead the consumer, for example when it fails to indicate clearly that saturated fat may result from hydrogenation of previously polyunsaturated vegetable fat.

Dietary Treatment of Specific Types of Hyperlipoproteinemia

Type I. The hyperchylomicronemia of Type I can be controlled by severe restriction of dietary fat intake to about 25 to 35 grams per day in the adult and 15 grams per day in the child. Alcohol should be banned. No special control of dietary cholesterol intake is required, nor is weight control relevant. No drug is known to be effective in Type I. Medium-chain triglyceride (MCT), which does not depend on chylomicron formation for its absorption, may be used to render the diet more palatable. Adherence to a low-fat regimen markedly lowers the levels of the triglyceride-rich chylomicrons which characterize this rare disorder, and leads to resolution of hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, and most importantly, attacks of acute pancreatitis. Type I subjects do not appear to be at special risk for coronary heart disease.

Type IIa. The dietary management of Type IIa, one of the most common hyperlipoproteinemias, consists of restriction of cholesterol intake to less than 300 mg per day and fat intake to less than 30 per cent of dietary calories. Saturated fat is especially restricted; some of the saturated fat may be replaced by polyunsaturated fat so that a P : S ratio of about 2.0 is obtained. No special polyunsaturated fat supplements are indicated. Weight restriction is not a necessary compo-

nent of the Type IIa regimen. The Type IIa diet is not unduly difficult to adhere to, since it does not restrict calories, and since many new recipes and allowable foods have been developed.

The low-cholesterol, low-saturated-fat regimen can be expected to reduce total plasma cholesterol by 15 to 20 per cent when rigorously applied (for example, in the metabolic ward). Typically, reductions of 10 to 15 per cent are seen in the free-living situation. In clear-cut familial hypercholesterolemia, the cholesterol reduction by diet is usually insufficient, especially in adults, to bring cholesterol levels into the normal range. Subjects with other forms of primary Type IIa often show a more impressive response with normalization of their cholesterol levels. It is possible to further reduce total cholesterol (and LDL) levels in Type IIa subjects by the addition of a biliary sequestrant such as cholestyramine or colestipol. Combined diet and drug therapy typically leads to a 40 per cent reduction in total plasma cholesterol and will produce normal levels in the majority of Type IIa subjects. Subjects with Type IIa have a greatly increased risk of coronary heart disease. The ability to lower LDL cholesterol in such subjects by combined diet and drug treatment is extremely encouraging. It is hoped that the Lipid Research Clinics Type II Coronary Primary Prevention Trial will establish whether such treatment is beneficial.[23]

Types IIb and III. Overweight subjects should embark on a weight reduction regimen followed by a maintenance diet providing protein, fat and carbohydrate in the proportions 20 : 40 : 40. Cholesterol should be restricted to less than 300 mg per day. Alcohol is inadvisable. In Type III subjects this diet results in dramatic falls in plasma triglyceride and cholesterol levels. Additional reductions may be obtained by use of clofibrate or nicotinic acid. Since (a) Type III is often associated with premature vascular (coronary, peripheral) disease, (b) the degree of lipid-lowering that can be obtained by combined diet and drug treatment is so dramatic and is accompanied by xanthoma resolution, and (c) peripheral vascular blood flow reportedly improves as a result, most physicians advocate aggressive treatment of Type III subjects.

Type IV. Subjects with a primary increase of VLDL are usually overweight, and the first element of diet is weight reduction. This alone often results in markedly reduced triglyceride levels. When normal weight is obtained, a maintenance regimen (20 : 40 : 40) should be adhered to. Steps have to be taken to insure that the reduction in the percentage of calories derived from carbohydrates does not result in an increased fat intake. Dietary cholesterol is restricted to 300 to 500 mg per day. Alcohol is best avoided.

Since, as mentioned earlier, it is unclear whether triglyceride is an independent risk factor for coronary heart disease, and since dietary therapy is effective in most Type IV subjects, one should consider supplementing diet therapy with drugs such as clofibrate only in those subjects with severe hypertriglyceridemia (especially if they have a family history of premature coronary heart disease).

Type V. This uncommon but potentially dangerous form of hyperlipoproteinemia is often effectively controlled by dietary measures. Most

subjects are overweight, and weight reduction followed by a maintenance regimen often reduces triglyceride levels sufficiently to avoid pancreatitis and its sequelae. The maintenance regimen should be relatively low in fat to control chylomicronemia and low in carbohydrate to control the raised VLDL levels. Alcohol is not at all permitted. If dietary measures are insufficient, then various drugs may be tried such as nicotinic acid, clofibrate, and progestational analogs; however, there are often problems in selecting drugs for Type V subjects; for example, pre-existing hyperuricemia or impaired glucose tolerance may contraindicate the use of nicotinic acid.

Dietary Change in the Population

As indicated earlier, there is much evidence to suggest that industrialized and affluent populations such as the United States have cholesterol distributions higher than those of countries where coronary heart disease is not so prevalent. Further, dietary fat intake appears to be unduly high in the United States, and fat restriction would lead to a downward shift of the cholesterol distribution. Although subjects at the upper end of the cholesterol distribution are at greatest risk for coronary heart disease, much coronary heart disease occurs throughout the cholesterol distribution. Reduction of cholesterol from any given "United States level" might be associated with a reduction of risk for coronary heart disease. These are some of the considerations which have led many expert bodies to recommend that Americans alter their dietary fat intake. A recent well-publicized example of this is the "Dietary Goals" of the United States Senate Select Committee on Nutrition and Human Needs,[36] which recommended that the United States population reduce the number of calories derived from fat to 30 per cent from its present level of approximately 40 per cent; reduce consumption of saturated fat to 10 per cent of total calories; balance monounsaturated and polyunsaturated fat intake each to 10 per cent of total calories; and reduce cholesterol intake to about 300 mg per day. If the levels of association between cholesterol and coronary heart disease observed in the Framingham Study are used as a basis for projection as to what could be achieved by cholesterol-lowering, then a 1 per cent reduction in cholesterol might produce a 2.5 per cent reduction in coronary mortality, and a 10 per cent reduction should lead to a 25 per cent fall. This exemplifies the substantial reduction in deaths that might result from relatively modest falls in cholesterol achieved by fairly simple changes in diet.

Possible Risks of Dietary Changes

One must consider the possibility that some risks may be associated with modifying dietary fat intake along the lines recommended. An increased incidence of deaths from malignant disease was reported by Pearce et al.[29] in a group of older men treated with a cholesterol-lowering diet, in which the 40 per cent of calories (fat) was mainly derived from polyunsaturated vegetable sources. However, further analysis of this and several other diet studies did not reveal a significant increase in malignant deaths.[10] Further, in a study of Finnish

mental hospital patients treated with a high-polyunsaturated-fat diet, an insignificantly higher mortality rate from malignant disease was found.[35] There is thus little evidence linking a high-polyunsaturated-fat diet with malignant neoplasms. It should also be noted that current cholesterol-lowering regimens emphasize restricting saturated fat more than increasing polyunsaturated fat intake.

It has also been suggested that a high-polyunsaturated-fat diet may lead to gallstones.[8] There is conflicting evidence whether the components of such a diet result in a lithogenic bile. There is a need for better information on these questions.

Current Stances on Dietary Change in the Population

We can conveniently, if rather simplistically, identify three schools of thought surrounding the question of dietary change in the United States today. First, there are those who are unconvinced by the dietary cholesterol–blood cholesterol–coronary heart disease relationships and who do not believe that there is any justification for considering any change. These must be regarded as being in a minority and having a point of view hardly supportable by the facts.

Second, there are those who are convinced that cholesterol is intimately related to coronary heart disease. However, this group is still troubled by the many important gaps in our understanding of lipid and lipoprotein metabolism and its relationship to atherogenesis and coronary heart disease, and is reluctant to advocate widespread change until a better picture emerges. This point of view has been recently supported by the emergence of the inverse risk factor status of high density lipoprotein and the growing information that HDL levels are also influenced by dietary factors. Thus, it will be necessary to review current dietary recommendations to see to what extent they can be reconciled with measures for obtaining optimal HDL levels. Furthermore, this second group is apprehensive about recommending change until at least one well-conducted study has demonstrated unequivocal benefit of cholesterol-lowering. The widespread economic and social consequences of substantially altering diet act as a further inhibition to recommending change until these requirements are met.

Third, there are those who argue, cogently, that the evidence presently available is sufficient justification for embarking upon the various measures which could reduce population blood cholesterol levels. In addition, they point that such change would appear to be safe and would also reflect a reversal of dietary changes in the opposite direction which have been occurring as a result of social and economic forces.

Whatever the final outcome of this debate, it is inevitable that some form of dietary change along the lines described will be a component of the various lifestyle changes which will be required to reduce the appalling toll from coronary heart disease. The recent substantial decline in cardiovascular mortality highlights that atherosclerotic coronary heart disease need not be regarded as an inevitable accompaniment of the type of culture we have constructed, but can be influenced by social and therapeutic measures.

ACKNOWLEDGMENT

The authors thank Mrs. Janet Bungay for editorial assistance and Mrs. Karen Wishnow for manuscript preparation.

REFERENCES

1. Ashley, F. W., Jr., and Kannel, W. B.: Relation of weight change to changes in atherogenic traits. The Framingham Study. J. Chron. Dis., *27*:103–114, 1974.
2. Blackburn, H.: Diet and mass hyperlipidemia. A public health view. *In*. Levy, R. I., et al., eds.: Nutrition, Lipids, and Coronary Heart Disease. New York, Raven Press, 1979, pp. 309–348.
3. Castelli, W. P., Doyle, J. T., Gordon, T., et al.: Alcohol and blood lipids. The Cooperative Lipoprotein Phenotyping Study. The Lancet, 2:153–155, 1977.
4. Committee of Principal Investigators: A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. Brit. Heart J., *40*:1069–1118, 1978.
5. Cooper, R., Stamler, J., Dyer, A., et al.: The decline in mortality from coronary heart disease; U.S.A., 1968-1975. J. Chron. Dis., *31*:709–720, 1978.
6. Cornfield, J., and Mitchell, S.: Selected risk factors in coronary disease. Possible intervention effects. Arch. Environ. Health, *19*:382–394, 1969.
7. Coronary Drug Project Research Group: The Coronary Drug Project. Clofibrate and niacin in coronary heart disease. J.A.M.A., *231*:360–381, 1975.
8. Dayton, S., Pearce, M. L., Hashimoto, S., et al.: A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation, *40* (Suppl. 2):1–63, 1969.
9. Diet-Heart Review Panel: Mass field trials of the diet-heart question. New York, American Heart Association Monograph No. 28, 1969, 51 pp.
10. Ederer, F., Leren, P., Turpeinen, O., et al.: Cancer among men on cholesterol-lowering diets. The Lancet, 2:203–206, 1971.
11. Frederickson, D. S., Levy, R. I., Bonnell, M., et al.: Dietary Management of Hyperlipoproteinemia — A Handbook for Physicians and Dietitians. Washington, D.C., U.S. Department of Health, Education, and Welfare, Publication No. (NIH) 75-110, 1974, 95 pp.
12. Fredrickson, D. S., Levy, R. I., Lees, R. S.: Fat transport in lipoproteins — an integrated approach to mechanisms and disorders. New Engl. J. Med., *276*:32–44, 94–103, 148–156, 215–226, 273–281, 1967.
13. Garcia-Palmieri, M. R., Tillotson, J., Cordero, E., et al.: Nutrient intake and serum lipids in urban and rural Puerto Rican men. Amer. J. Clin. Nutr., *30*:2092–2100, 1977.
14. Gordon, T.: The Framingham Diet Study. Diet and the regulation of serum cholesterol. *In* The Framingham Study — An Epidemiological Investigation of Cardiovascular Diseases. Washington, D.C., U.S. Department of Health, Education and Welfare, 1970 Section 24.
15. Gordon, T., Kagan, A., Garcia-Palmieri, M. R., et al.: Diet and its relation to coronary heart disease and death in three populations. In preparation.
16. Gotto, A. M., Jr., Shepherd, J., Scott, L. W., et al.: Primary hyperlipoproteinemia and dietary management. *In* Levy, R. I., et al., eds.: Nutrition, Lipids, and Coronary Heart Disease. New York, Raven Press, 1979, pp. 247–284.
17. Hegsted, D. M., McGandy, R. B., Myers, M. L., et al.: Quantitative effects of dietary fat on serum cholesterol in man. Am. J. Clin. Nutr., *17*:281–295, 1965.
18. Kannel, W. B., Castelli, W. P., and Gordon, T.: Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham Study. Ann. Intern. Med., *90*:85–91, 1979.
19. Kagan, A., Harris, B. R., Winkelstein, W., Jr., et al.: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California. Demographic, physical, dietary and biochemical characteristics. J. Chron. Dis., *27*:345–364, 1974.
20. Keys, A., ed.: Coronary heart disease in seven countries. Circulation, *41*(Suppl. I):1970.
21. Keys, A., Anderson, J. T., and Grande, F.: Prediction of serum cholesterol responses of man to change in fats in the diet. The Lancet, 2:959–966, 1957.
22. LaRosa, J. C.: Secondary hyperlipoproteinemia. *In* Rifkind, B. M., and Levy, R. I., eds.: Hyperlipidemia: Diagnosis and Therapy. New York, Grune & Stratton, 1977, pp. 205–216.

23. Lipid Research Clinics Program: The Coronary Primary Prevention Trial. Design and implementation. J. Chron. Dis., in press, 1979.
24. Lipid Research Clinics Program Epidemiology Committee: Plasma lipid distributions in selected North American populations: The LRC Program Prevalence Study. Circulation, 60:427–439, 1979.
25. Little, J. A., McGuire, V., and Derksen, A.: Available carbohydrates. *In* Levy, R. I., et al.: Nutrition, Lipids, and Coronary Heart Disease. New York, Raven Press, 1979, pp. 119–148.
26. Liu, K., Stamler, J., Dyer, A. et al.: Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. J. Chron. Dis., 1978.
27. McGill, H. C., Jr., ed.: Geographic Pathology of Atherosclerosis. Baltimore, Williams and Wilkins, 1968.
28. McNutt, K. W.: Nutrition labeling — a tool for diet planning. *In* Levy, R. I., et al.: Nutrition, Lipids and Coronary Heart Disease. New York, Raven Press, 1979, pp. 425–440.
29. Pearce, M. L., and Dayton, S.: Incidence of cancer in men on a diet high in polyunsaturated fat. The Lancet, *1*:464–467, 1971.
30. Phillips, R., Lemon, F., and Kuzma, J.: Coronary heart disease mortality among Seventh-Day Adventists with differing dietary habits. A preliminary report. Amer. J. Clin. Nutr., *31*(10 suppl.):S191–S198, 1978.
31. Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. J. Chron. Dis., *31*:201–306, 1978.
32. Roth, H. P., and Mehlman, M. A., eds.: Proceedings of the symposium on Role of Dietary Fiber in Health. Amer. J. Clin. Nutr., *31* (10 Suppl.):S1–S291, 1978.
33. Shank, R. E.: Nutrition in relation to other aspects of cardiovascular disease. *In* Levy, R. I., et al., eds.: Nutrition, Lipids, and Coronary Heart Disease. New York, Raven Press, 1979, pp. 523–553.
34. Stamler, J.: Population studies. *In* Levy, R. I., et al., eds.: Nutrition, Lipids, and Coronary Heart Disease. New York, Raven Press, 1979, pp. 25–88.
35. Turpeinen, O.: Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes. Circulation, 59:1–7, 1979.
36. U.S. Senate Select Committee on Nutrition and Human Needs: *Dietary Goals for the United States*. Washington, D.C.: U.S. Government Printing Office, 1978.
37. Yudkin, J., and Roddy, J.: Levels of dietary sucrose in patients with coronary atherosclerotic disease. The Lancet, 2:6–8, 1964.
38. Zilversmit, D. B.: Dietary fiber. *In* Levy, R. I., et al., ed.: Nutrition, Lipids, and Coronary Heart Disease. Raven Press, 1979, pp. 149–174.

National Heart, Lung and Blood Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20205

Nutritional Management of Diabetes

Gerald M. Reaven, M.D., Ann M. Coulston, M.S., R.D.,** and Robert A. Marcus, M.D.****

In this presentation we will review recent information concerning the nutritional management of patients with diabetes mellitus. The importance of this topic cannot be overestimated, and there is no more relevant therapeutic issue than diet to be considered in these patients. Unfortunately, there are few issues in which there are greater differences of opinion, and, at the present time, it is unlikely that any given point of view can be considered to be the "correct" one. On the other hand, although the answers may not be unequivocal, the questions that need to be asked are well-recognized. We will attempt to address these questions, using the information we feel is most applicable to the role of diet in the treatment of patients with diabetes mellitus. In so doing, we will rely entirely on information obtained from studies of man. Although we are well aware of the wealth of data available from study of experimental animals, its relevance to man may be questionable. Given the state of confusion in these matters, it seemed best to avoid this additional dilemma.

We think it essential that any discussion of the treatment of diabetes begin by acknowledging the fact that patients with diabetes can no longer be considered to represent a homogenous group. Patients currently classified as having diabetes mellitus differ greatly in any number of important characteristics, and for purposes of this presentation we will arbitrarily divide them into three categories. The first group will consist of individuals without fasting hyperglycemia (fasting

Division of Gerontology, Department of Medicine, Stanford University School of Medicine, and Geriatric Research, Education and Clinical Center, Veterans Administration Medical Center, Palo Alto, California.

*Professor of Medicine, Stanford University School of Medicine and Director, Geriatric Research, Education and Clinical Center, Veterans Administration Medical Center, Palo Alto

**Research Dietitian, General Clinical Research Center, Stanford University School of Medicine

***Assistant Professor of Medicine, Stanford University School of Medicine

This work is supported by grants from the National Institutes of Health, HL 08506 and from the General Clinical Research Centers Branch, RR-70, and from the Research Services of the Veterans Administration.

plasma glucose concentration ≤125 mg per dl), who are considered to have an abnormal glucose tolerance test (chemical diabetes). The second category will comprise patients whose fasting plasma glucose concentrations exceed 125 mg per dl, but who have nonketotic, insulin-independent diabetes mellitus. This group will include patients who, in addition to diet, may require oral agents or insulin to control their hyperglycemia. The third category will consist of patients with ketosis-prone, insulin-dependent diabetes. Within all three groups we will limit our comments to the dietary management of adults in order to avoid the complex series of nutritional issues that face the diabetic child who is still actively growing. Although these are obviously important matters, they cannot be given appropriate consideration within the space constraints of this presentation.

The topics we have selected for consideration are: obesity; the relative amount as well as the kind of dietary carbohydrate and fat; and dietary fiber. In each case we will address not only the relationship of the particular issue to glucose regulation, but also its impact on lipoprotein metabolism. Our justification for considering lipoprotein metabolism in establishing a diabetic diet is based upon the following: (1) atherosclerosis is a primary cause of morbidity and mortality in patients with diabetes; (2) abnormal lipoprotein metabolism is recognized to be an important risk factor in the development of vascular disease; and (3) manipulation of the amount and/or kind of foodstuffs is the preferred way to modify plasma lipid concentrations. Hypertriglyceridemia has been said to be "the hyperlipidemia par excellence of the diabetic."[5] Given the evidence linking hypertriglyceridemia to the development of atherosclerosis in patients with diabetes,[66] efforts aimed at control of plasma very low density lipoprotein (VLDL)-triglyceride (TG) levels in patients with diabetes would seem to be warranted. Whether or not the incidence of hypercholesterolemia is increased in diabetics has been more controversial.[54] On the other hand, even if hypercholesterolemia is not characteristic of diabetics as a group, it still seems prudent to maintain low density lipoprotein (LDL)-cholesterol levels as low as possible in these subjects. Indeed, this is the major reason for the interest in increasing the proportion of carbohydrate in the diabetic diet, i.e., an attempt to lower plasma LDL-cholesterol levels by the reciprocal decrease in dietary fat intake.

Our goal has been to develop an approach to the dietary management of the individual patient with diabetes which is both practical and based upon experimental evidence which can be evaluated by the reader. It is our hope that this program will help the physician achieve optimal control of both hyperglycemia and hyperlipoproteinemia in patients currently classified as having diabetes mellitus.

OBESITY

Obesity is widely recognized as a fundamental consideration in the majority of adult diabetics. In the University Group Diabetes Program (UGDP) study population, 55 per cent of all patients, and 63 per cent

of women exceeded desirable body weight by more than 25 per cent.[76] It is no surprise, therefore, that restriction of calories in order to achieve ideal weight has been repeatedly stressed as the single most important component of the dietary management of diabetes.[1]

Carbohydrate Metabolism

It has been known for some time that obesity leads to a loss of normal insulin sensitivity,[60] and more recent data indicate that this is associated with a reduction in number of insulin receptors.[10, 20, 57] At present, the relationship between these two variables is not clear. Obviously, a loss of insulin receptors secondary to obesity could account for the development of insulin resistance. Alternatively, it has been suggested that the decrease in number of insulin receptors seen in obese individuals is secondary to the hyperinsulinemia that characterizes these subjects.[10] Irrespective of which of these two formulations ultimately prevails, it is obvious that the presence of these metabolic abnormalities can account for the glucose intolerance associated with the obese state.

In obese patients with chemical diabetes, insulin secretory responses continue to be greater than those seen in either nondiabetic lean or obese subjects.[19, 67] However, as the degree of glucose intolerance increases, the plasma insulin response eventually attenuates, so that obese patients with severe fasting hyperglycemia may have plasma insulin responses to oral glucose which are lower than normal.[62, 67]

Given the profound effect of obesity on carbohydrate metabolism, it is not surprising that weight loss has been the foundation of therapy for the diabetic patient. Recent evidence supports the clinical impression that weight loss alone can reverse the abnormalities in carbohydrate metabolism regardless of their severity. Thus, improvement in glucose tolerance and reduction in insulin hypersecretion was noted in a group of moderately obese chemical diabetics as the result of a 20 pound weight loss.[55] Similar improvement has also been described for patients with greater degrees of fasting hyperglycemia.[21, 30] In fact, in one large study which attempted to evaluate the efficacy of oral hypoglycemic agents, an initial period of diet so successfully reversed the chemical abnormalities that it was unnecessary to proceed with the drug phase of the protocol.[30] Weight loss has also proven to be effective therapy in obese patients with severe fasting hyperglycemia and insulin deficiency, though the mechanisms by which benefits accrue remain uncertain. Indisputably, resistance to insulin decreases.[28] However, recent evidence[72] suggests that some increase in insulin secretory capacity may also be associated with the dramatic improvement which is seen following weight loss. Finally, the potential important role of obesity in patients with insulin-dependent, ketosis-prone diabetes should not be ignored. Although gross obesity is rare in these patients, an increase over ideal body weight can occur. In this situation there is every reason to believe that a return to ideal body weight would improve both insulin sensitivity and glucose tolerance.

Lipid Metabolism

The association between hypertriglyceridemia and obesity is generally acknowledged.[5] Furthermore, it has been shown that weight gain leads to a rise in plasma triglyceride levels,[70] and that plasma triglyceride concentrations fall when patients lose weight.[57] It has been suggested that hypertriglyceridemia in obese patients is a consequence of peripheral resistance to insulin, leading to hyperinsulinemia and an increase in hepatic synthesis and secretion of VLDL-TG[55]. A similar sequence of events appears to account for hypertriglyceridemia in nonobese patients with chemical diabetes,[25, 56, 61] and it is obvious that obesity would accentuate the situation in these patients. Increased turnover of plasma free fatty acids has been shown to correlate significantly with excess weight,[52] and this phenomenon could certainly contribute to the increased VLDL-TG secretion seen in patients with chemical diabetes. An increase in free fatty acid turnover may play an even more important causal role in the increased VLDL-TG secretion and hypertriglyceridemia seen in insulin-independent patients with significant hyperglycemia.[29, 45] Although the effects of obesity on cholesterol metabolism are substantial, they result less often in increased circulating levels of cholesterol. Nonetheless, it is clear that obese patients have increased cholesterol turnover rates, and expanded total body exchangeable cholesterol pools.[49, 53]

Given the hyperlipidemic effect of obesity, it would seem reasonable to assume that weight loss would lead to a fall in plasma lipid elevations in diabetic subjects. Although there is considerable clinical support for this notion, relatively few systematic studies of this problem have actually been reported. Weight loss of 20 pounds in patients with chemical diabetes resulted in a decrease in insulin resistance, plasma insulin levels, VLDL-TG secretion rate, and plasma triglyceride concentrations.[55] Plasma cholesterol concentrations also were reduced following the weight loss. It is interesting to note that the improvement in patients who were still obese after the 20 pound weight loss was as striking as it was in those individuals who regained ideal body weight as the result of the same degree of weight loss. Thus, it was weight loss *per se* which accounted for the metabolic improvement. One would also expect similar changes to occur in patients with insulin-independent diabetes and significant hyperglycemia, but this issue has not been systematically investigated. Neither obesity nor hyperlipidemia is commonly observed in insulin-dependent diabetic subjects who are receiving insulin.[29, 54]

DIETARY CARBOHYDRATE

Effect of Variations in Dietary Carbohydrate Intake on Carbohydrate Metabolism

In 1936 Himsworth[31] demonstrated that "the greater the amount of carbohydrate in the diet, the greater the sensitivity of the organism to insulin." The potential importance of this observation to the treat-

ment of patients with diabetes seemed to escape attention for many years, and dietary management of diabetes has emphasized carbohydrate restriction. However, the recent trend has been to liberalize dietary carbohydrate intake in patients with diabetes mellitus,[1] and in the past few years it has been suggested that diabetic patients might actually benefit from the institution of high carbohydrate diets.[16, 41, 73] Thus, the first question that must be addressed is the effect of differences in amount of dietary carbohydrate on carbohydrate homeostasis in patients with various kinds of diabetes.

CHEMICAL DIABETES. It has been suggested that the plasma glucose response to a standard oral glucose challenge is improved if patients with chemical diabetes ingest a high carbohydrate (75 to 85 per cent of total calories) diet for several days.[6, 16] The improvement in oral glucose tolerance was associated with a fall in the plasma insulin response to the glucose challenge, supporting the observation of Himsworth that insulin sensitivity improves following the ingestion of a high carbohydrate diet. Since loss of normal insulin sensitivity seems to characterize patients with chemical diabetes,[61] a high carbohydrate diet would seem to be the treatment of choice in these subjects.

On the other hand, the benefit of greatly increasing carbohydrate in patients with chemical diabetes may be more apparent than real. Thus, Anderson[6] indicated that the area circumscribed by the plasma glucose concentrations during the oral glucose tolerance test was not significantly lower after several days on a 75 per cent carbohydrate diet. Using a similar measurement, Brunzell et al.[16] demonstrated that 8 to 10 days of an 85 per cent carbohydrate diet led to a mean improvement in carbohydrate tolerance of 8 per cent. These results demonstrate that marked increases in carbohydrate intake lead to marginal improvements in plasma glucose response during an oral glucose tolerance test. Furthermore, the improvement was gained at the expense of an approximate doubling of an individual's carbohydrate intake, i.e., from 40 to 45 per cent to 75 to 85 per cent of total calories. Since increasing daily dietary carbohydrate intake by only 12 to 15 per cent led to significant elevations of postprandial plasma glucose concentration,[26, 63] increasing daily carbohydrate intake by 40 per cent will ensure that such patients have day-long elevations of their plasma glucose levels. Furthermore, elevations in postprandial glucose concentrations produced by high carbohydrate diets will lead to concomitant elevations of plasma insulin level,[25, 26, 61] and the implication of this in the development of hypertriglyceridemia will be discussed in a subsequent section.

INSULIN-INDEPENDENT DIABETES. Although it was pointed out several years ago that diabetic control could be maintained with sulfonylurea compounds in patients ingesting approximately 65 per cent of total calories as carbohydrate,[58] we are only aware of three controlled studies which have evaluated the effects of variations in carbohydrate intake on diabetic control. Weinsier and colleagues[77] noted that increasing dietary carbohydrate from approximately 40 to 55 per cent did not lead to deterioration of diabetic control. However, fasting plasma glucose concentration exceeded 125 mg per dl in only 10 of the

18 patients they studied and the only two patients with fasting glucose levels in excess of 200 mg per dl demonstrated a two to three-fold increase in 24 hour urine glucose excretion on the 55 per cent carbohydrate diet. Kiehm et al.[41] increased dietary carbohydrate from 43 to 75 per cent in 13 diabetic patients who had been treated with either insulin or sulfonylurea agents. Three of the 13 patients were taking 40 to 55 units of insulin, and the dietary changes did not appear to benefit these subjects. However, in the other 10 patients the 75 per cent carbohydrate diet led to a mean fall in fasting plasma glucose concentration, associated with a reduction or even cessation of insulin or sulfonylurea agents. Finally, when Brunzell and colleagues[17] increased dietary carbohydrate intake from 45 to 85 per cent in 11 untreated insulin-independent diabetics, fasting hyperglycemia increased in 8 subjects and glycosuria worsened in 9. In general, the more severe the degree of fasting hyperglycemia, the greater the deterioration of glucose tolerance. In contrast, the high carbohydrate diet did not lead to a deterioration of glucose tolerance in 9 comparable patients who were receiving concomitant treatment with either insulin or sulfonylurea compounds. Indeed, fasting plasma glucose levels fell slightly, and insulin doses were decreased in two subjects.

The reasons for the differences in the efficacy of the high carbohydrate feeding among the three studies are not immediately apparent, although several possibilities can be considered. In the first place, the patients described by Kiehm et al.[41] underwent a statistically significant fall in body weight during the high carbohydrate feeding, and the beneficial effect of weight loss in improving glucose tolerance and insulin sensitivity is well-documented.[55] Secondly, the amounts of insulin and sulfonylurea compounds "required" to control plasma glucose levels are often not requirements at all, but simply represent the amount a patient is receiving. Under these conditions it is often possible to decrease these doses, and the study of Kiehm et al.[41] suffers from the lack of an after control, i.e., an attempt to see how well the patients did when they were placed back on their original diet (43 per cent carbohydrate) after their doses of insulin and oral agents had been lowered. Thirdly, it must be appreciated that the high carbohydrate diet used by Kiehm and associates[41] featured natural foods and was high in fiber, in contrast to the high carbohydrate, liquid formula diet of Brunzell et al.[17] However, the patients followed by Weinsier et al.[77] were also eating food, and a dietary carbohydrate intake of approximately 55 per cent led to significant worsening of diabetic control in the few patients with glucose levels in excess of 200 mg per dl. Perhaps the increased fiber content played an important role in preventing postprandial hyperglycemia when dietary carbohydrate was increased by Kiehm et al.[41] In any event, the potential ability of a high carbohydrate diet to improve insulin sensitivity must be balanced against the effect that increases in dietary carbohydrate intake have on postprandial glucose levels. In this regard, it is essential to note that Lenner[48] has clearly indicated that postprandial plasma glucose responses of sulfonylurea-treated adult diabetic patients doubled when

the carbohydrate contents of a test breakfast was increased from approximately 33 to 60 per cent of total calories. This study was carried out with real food, and once again emphasizes the fact that increases in dietary carbohydrate can significantly elevate postprandial plasma glucose levels. If the goal of dietary management in diabetic patients is to minimize hyperglycemia, the therapeutic utility of a high carbohydrate diet will depend upon its ability to improve insulin sensitivity more than it leads to higher postprandial glucose levels. The data reviewed to date do not prove that this is the case.

INSULIN-DEPENDENT DIABETES. Two studies[12, 73] of such patients have demonstrated that a high carbohydrate diet does not lead to a change in either degree of diabetic control or an increase in insulin dose. Furthermore, Lenner has pointed out that there were no differences in the postprandial glucose responses of insulin-dependent diabetics to test breakfasts ranging widely in carbohydrate content.[18] Indeed, the height of the postprandial glucose response was more dependent upon fasting glucose level than it was on amount of dietary carbohydrate. If one takes into account the intrinsic chaotic nature of plasma glucose levels in insulin-dependent patients,[69] the fact that diabetic control and insulin requirements do not appear to change with variations in carbohydrate intake may not be too surprising.

Effect of Variations in Dietary Carbohydrate on Lipid Metabolism

Changes in amount of dietary carbohydrate in isocaloric diets involve reciprocal changes in amount of dietary fat, and the potential effect of these related manipulations on lipoprotein metabolism will be discussed in this section. The effect of changes in the kind of dietary fat will be considered subsequently.

CHEMICAL DIABETES. It has been known for some time that increases in dietary carbohydrate intake will lead to elevations of VLDL-TG concentration,[3, 25] and that the cause of the hypertriglyceridemia in this situation is an increase in VLDL-TG secretion rate.[61] Although controversy remains concerning the cause of the increase in VLDL-TG secretion, a large body of evidence strongly suggests that it is secondary to elevated plasma insulin levels.[56] Thus, the ingestion of a high carbohydrate diet by patients with chemical diabetes would be expected to stimulate VLDL-TG secretion, and lead to hypertriglyceridemia. This expectation has been realized, and fasting hypertriglyceridemia has been regularly observed when dietary carbohydrate is increased in patients with mildly abnormal glucose tolerance.[17, 25, 46, 61] The cholesterol levels in these studies were essentially unchanged. These results suggest that the use of high carbohydrate diets in patients with chemical diabetes would have deleterious effects on lipoprotein metabolism. However, the contrary has been argued.[16] It has been suggested that the ability of high carbohydrate diets to increase plasma VLDL-TG levels is likely to be a temporary phenomenon, and that plasma TG levels will return to normal with continued use of the high carbohydrate diet.[16] Unfortunately, the transient nature of carbohydrate-induced increases in VLDL-TG levels is not supported by a great deal of experi-

mental data. One study,[47] which is widely quoted in this regard, was published as an abstract in 1965, and states "that hypertriglyceridemia *diminished* by 7 to 14 days despite continuation of high carbohydrate intake." Other, relatively short-term, studies (up to 12 weeks) also suggest that carbohydrate-induced hypertriglyceridemia may *diminish* with time, but in none of these have TG levels actually returned to baseline values. Indeed, the only documented evidence that high carbohydrate diets do not produce a sustained increase in plasma TG levels is found in the study of Antonis and Bersohn,[8] carried out on South African prisoners. However, the application of these data observed in normal subjects with extremely low VLDL-TG levels to the situation in diabetic patients with hypertriglyceridemia is questionable.

Another argument for the use of high carbohydrate diets acknowledges the fact that such a diet will increase fasting triglyceride levels, but states that the lower fat content of these diets will result in lower postprandial, and therefore lower 24 hour integrated, plasma triglyceride concentrations.[16] However, it would appear that the two diets being compared must be very disparate in order for low-fat diets to result in lower postprandial triglyceride levels. For example, Schlierf et al.[68] compared a diet of less than 5 per cent fat with one of 65 per cent fat in order to establish this point, while Moser and Anderson[51] compared diets containing 40 versus 75 percent carbohydrate. Although not stated, the fat content must have been quite low on the 75 per cent carbohydrate diet. It is not surprising that such extremely low-fat diets result in a diminished postprandial triglyceride response, since there will be essentially no chylomicronemia on such low-fat diets. The relevance of this degree of dietary fat restriction to day by day life is questionable, particularly when increasing dietary carbohydrate by only 15 per cent (from 40 to 55 per cent of total calories) resulted in an increase in both fasting and postprandial triglyceride levels.[26] Taking all of these considerations into account, it would appear that it is difficult to establish a beneficial effect of high carbohydrate (low fat) diets on serum trigylceride and cholesterol levels in patients with chemical diabetes.

INSULIN-INDEPENDENT DIABETES. A considerable number of these patients are still capable of increasing insulin secretion in response to dietary carbohydrate, and it has been shown that the ingestion of an 85 per cent carbohydrate diet will lead to hypertriglyceridemia in proportion to the rise in postprandial insulin levels.[61] However, the use of a 55 per cent carbohydrate diet did not lead to a change in either fasting plasma triglyceride levels or cholesterol levels in a group of outpatients studied by Weinsier et al.,[77] and Kiehm et al.[41] have reported that a 75 per cent carbohydrate diet led to a fall in both cholesterol and triglyceride concentrations. Although the insulin levels were not reported in the latter two studies, it would appear that at least some of the patients were capable of endogenous insulin secretion. The differences noted in the effects of increasing dietary carbohydrate intake on the plasma triglyceride and cholesterol level are likely to have resulted

from differences between the studies which involved amount of dietary carbohydrate (and fat), kind of dietary fat, amount of fiber, food versus formula, kind of dietary carbohydrate, etc. Unfortunately, the differences are too many, and the information too sparse, to permit reconciliation of these data at this time.

INSULIN-DEPENDENT DIABETES. There are two published studies documenting the effects of high carbohydrate diets on lipid levels in such patients, and the results are quite different. Thus, Bierman and Hamlin[12] noted that increasing dietary carbohydrate from 45 to 85 per cent of total calories led to a striking increase in triglyceride levels, without any change in cholesterol levels. In contrast, Stone and Connor[73] found that increasing dietary carbohydrate from 41 to 64 per cent led to a fall in cholesterol level, without a significant change in triglyceride concentration. The difference between the two studies may simply be a reflection of a 64 per cent as compared to an 85 per cent carbohydrate diet. On the other hand, Bierman and Hamlin used liquid formula diets, while Stone and Connor employed food. Once again, this important variable needs to be evaluated.

DIETARY FAT

Effect of Variations in Dietary Fat Intake on Carbohydrate Metabolism

In contrast to the voluminous literature dealing with the effect of modifications in kind of dietary fat on lipid metabolism, information concerning the effects of such dietary changes on carbohydrate metabolism is scant. Furthermore, the available studies are, for the most part, uncontrolled and short-term. Thus, Kinsell reported improvement in blood glucose in two patients when polyunsaturated fat was substituted isocalorically for saturated fat.[44] However, neither the constancy of weight nor the duration of the changes was described. In a larger study, Houtsmuller[32] reported that isocaloric substitution of linoleate for butter (50 per cent of total calories) led to significant reduction in plasma glucose and insulin concentrations in insulin-independent diabetics and to lowered plasma glucose levels and insulin requirements in insulin-dependent patients.

Effect of Variations in Dietary Fat Intake on Lipoprotein Metabolism

There is ample evidence in nondiabetic subjects that increases in dietary polyunsaturated fat and/or decreases in dietary cholesterol content can lead to significant falls in both plasma triglyceride and cholesterol concentrations.[2, 11, 18, 43] Although reference has been made by the American Medical Association Committee on Food and Nutrition to the benefits of such a diet for diabetics,[59] there have been few reports to validate such a position. King et al. studied the effect of a 70 per cent corn oil diet in patients with diabetic retinopathy, and ob-

served decreases in total plasma lipids and cholesterol, as well as clearing of retinal exudates.[42] In addition, Kaufmann et al.[39] reported that a modified-fat diet (P/S = 1.0) resulted in reduced triglyceride and cholesterol levels in a large group of diabetic children attending a summer camp. Although such evidence must be considered preliminary, the results are sufficiently provocative to warrant more detailed study of the long-term consequences of modified-fat diets in diabetic subjects. In the absence of such data it is necessary at the present time to rely primarily on the information available from studies of subjects with normal glucose tolerance. In this regard it is interesting to note that subjects who remained hypertriglyceridemic after 6 months of a diet containing 18 per cent protein, 39 per cent fat and 43 per cent carbohydrate (P/S ratio = 1.5), achieved substantial reductions of plasma triglyceride and cholesterol levels when switched to a carbohydrate-restricted diet with the same P/S ratio (20 per cent protein, 30 per cent carbohydrate and 50 per cent fat).[33]

FIBER

Dietary fiber is generally defined as plant materials that resist the action of human digestive enzymes. Various non-nutritive and unrelated substances are included in the term: cellulose, hemi-cellulose, lignin, pectin, and gums. Food analysis tables commonly list the crude fiber content of foods. This term includes only material resistant to acid and alkali hydrolysis, and thus tends to be underestimate dietary fiber content. Methodology for determining dietary fiber has not been standardized, athough the fiber content of many common foods has been compiled.[71] The major sources of fiber in the diet are fruits and vegetables, both fresh and cooked, cereal grains, whole grain flours, and nuts.

During the past ten years, substantial interest has developed regarding the etiologic role of dietary fiber in the development of human disease, and the potential therapeutic role for fiber.[23] Primary use of fiber in recent years has been in the management of diverticular disease of the colon and irritable bowel syndrome.

Trowell[74] has suggested that fiber-depleted diets may lead to the development of diabetes. This hypothesis is based on epidemiologic studies of primitive societies in rural Africa, where diets contained large quantities of unrefined carbohydrates compared to those of Western Society, and where the incidence of diabetes was quite low. Although provocative, such data do not establish causation, since other important factors, primarily obesity, also varied fundamentally in prevalence in rural Africa as opposed to Western cultures. On the other hand, the improvement in glucose tolerance, decreased insulin secretion in response to glucose, and reduction in serum cholesterol concentration that has been observed in fiber-treated patients[15, 22, 37] suggest that the addition of fiber to the diabetic diet might be of great therapeutic importance.

Effect of Dietary Fiber on Carbohydrate Metabolism

The likelihood that dietary fiber would modify plasma glucose and insulin responses in patients with diabetes seems to be supported by available data. Jenkins et al.[36] indicated that both plasma glucose and insulin levels were lowered when insulin-independent diabetics ate a meal containing pectin and guar gum. Three insulin-dependent patients reported in the same study demonstrated decreases in the glucose response to the same test meal, and a similar decrease in glucose response in insulin-dependent patients has been reported by Goulder et al.[27]

Longer term studies of the effect of added dietary fiber on glucose homeostasis in diabetics have also been promising. Kiehm et al.[41] were able to show dramatic improvements in glucose tolerance in 10 of 13 insulin-independent diabetics following 2 weeks of a fiber-supplemented, high carbohydrate diet. However, the fact that the test diet differed in so many ways from the control diet makes it difficult to assess the effect of fiber in this situation. On the other hand, there is evidence in insulin-dependent patients that fiber-enriched diets, per se, can reduce 24 hour urine glucose excretion,[35] as well as decrease postprandial plasma glucose levels.[50] However, it must be emphasized that the studies reported to date have been short-term, and the results must be regarded as tentative. Clearly, there is need for long-term, controlled studies of this issue.

Effect of Dietary Fiber on Lipid Metabolism

Dietary fiber has also been reported to decrease serum lipids in the normal population.[40] Serum cholesterol decreased significantly following the addition of pectin or guar gum to the diet for two weeks, although wheat bran appeared to have no effect.[22, 35, 75] Only scanty information exists on such effects in diabetic patients. The studies of Kiehm et al.,[41] cited previously, reported reduction in serum cholesterol, but not triglycerides, in diabetics of all degrees of severity, following institution of a high carbohydrate, high fiber diet. However, the test diet was considerably lower in total fat and cholesterol than the control diet (9 per cent versus 36 per cent and 63 mg versus 539 mg, respectively), so it is difficult to attribute the change in cholesterol specifically to the added fiber. Further studies are required, where dietary fiber is manipulated as the sole variable, before any conclusion can be reached on the effects of added fiber on plasma triglyceride and cholesterol levels in the diabetic.

RECOMMENDATIONS

Control of Obesity

From the preceding discussion it is clear that achieving ideal weight should be considered a primary goal in the management of obese diabetics, regardless of the degree of metabolic severity. Howev-

er, the weight loss strategy should be tailored to the severity of the metabolic complications. Patients with moderate hyperglycemia risk no short-term deterioration, and can be managed as outpatients. The important goal is not rapid weight loss, but restructuring of eating habits, so that a new equilibrium is gradually achieved and maintained. We see no advantage, therefore, to drastic curtailment of calories. Although such approaches frequently produce short-term success, recidivism is certain without successful behavior modification. Therefore, our aim for these patients is limited to a weekly loss of 1 to 3 pounds. Since one pound of adipose tissue loss represents approximately 3500 Kcal, a 1000 Kcal daily deficit below maintenance levels should suffice to achieve this goal (assuming that maintenance energy requirements approximate 35 Kcal per kg per day).

For several reasons we recommend that the composition of the diet not be severely altered during weight loss. Patients who are placed on unusual "diets" are not likely to incorporate food consumption patterns necessary to maintain the new weight once the "diet" is completed. Moreover, evidence indicates that balanced-deficit dieting (that is, a ratio of carbohydrate, fat and protein of approximately 40:40:20) achieves superior results to those seen with low carbohydrate programs, both with respect to preservation of lean mass and loss of adipose tissue.[80]

Bistrian has noted the relatively poor results of balanced-deficit dieting in patients exceeding 130 per cent of ideal weight, and advocates a "protein-sparing modified fast," in which total calories are provided as high quality animal protein.[14] This and other semistarvation methods present definite medical risks, e.g., hypotension and potassium loss, which temper our enthusiasm. Nonetheless, patients who fail to lose sufficient weight on balanced restriction, and who do not pose serious contraindications for semistarvation, may reasonably be tried on such a regimen, provided that medical supervision is adequate, and that the protein administered is of high biologic value. Unfortunately, the latter criterion does not apply to most widely marketed liquid protein formulas, whose protein source is low in tryptophan and other essential amino acids.

In patients with severe hyperglycemia, or, more rarely, with profound elevations in plasma lipids, the imminent dangers of hyperosmolar coma or pancreatitis may compel short-term hospitalization for intensive weight loss. Restriction of total daily calories to 600 or less can lead to prompt resolution of hyperglycemia and clearing of excessive lipemia.[14, 29, 72] Remarkably, only modest weight loss suffices to produce major and persistent reductions in blood glucose and experience indicates that insulin or oral hypoglycemic medication can successfully be discontinued during the period of calorie restriction.[13] Protein-sparing modified fasts have been successfully employed in these patients, and in three patients studied, nitrogen balance appeared to have been maintained.[13] Such a finding represents a potentially important advantage over total fasting; however, the superiority

of this approach over equal degrees of balanced calorie restriction has not been established.

We and others have had experience with patients on long-term in-hospital weight loss. However, hospital costs and inadequacy of insurance coverage restrict the method only to such institutions as the Veterans Administration or clinical research units. Although patients appear to accept dietary intervention in the setting of a protected ward environment, return to the stresses of home or work quickly leads to resumption of previous eating habits. Of the patients reported by Greenfield et al.[29] and by Stanik and Marcus,[72] regain of weight was the rule, despite frequent follow-up visits with dietitians and continuous reenforcement of dietary principles. Nonetheless, patients who successfully maintain their reduced weight can have sustained lowering of plasma glucose.

Distribution of Calories

We recognize that a trend exists toward increasing dietary carbohydrate in the diabetic diet. However, for the reasons outlined earlier, we are not convinced that such modification is associated with improvement in day to day plasma glucose concentrations. In addition, there is a real risk that hypertriglyceridemia will develop if the increase in carbohydrate intake is substantial, and, contrary to the frequently expressed opinion, we are not aware of compelling evidence that such hyperlipidemia is transient. Therefore, we feel it is premature to endorse a wholesale increase in dietary carbohydrate intake, and suggest that patients be maintained on diets that contain (as per cent of total calories) between 15 and 20 per cent of protein, with the remainder of the calories divided equally between fat and carbohydrate. We recognize the possibility that additional experience with particular varieties of carbohydrate, such as those foods rich in fiber may ultimately allow liberalization of carbohydrate intake (and reduction of fat) without the risk of hyperglycemia and hypertriglyceridemia. However, at present the evidence seems too scanty to allow such a conclusion. Finally, given the increased incidence of atherosclerosis in patients with diabetes we believe that saturated fat should be replaced with polyunsaturated fat and the cholesterol content of the diet lowered. By increasing consumption of fish, poultry and polyunsaturated oils, and by decreasing intake of red meat, eggs, fat-containing dairy products, and hydrogenated fat, it is relatively easy to create diets with a P/S ratio of 1.0 to 1.5 and a cholesterol content of less than 300 mg per day. We feel that such a goal should be pursued in patients with diabetes.

Fiber

The improvement in glucose tolerance and serum cholesterol as reported suggests that an increase in dietary fiber is a reasonable recommendation for diabetic patients. A simple way to gradually increase dietary fiber is to choose high fiber foods within the diabetic carbohy-

drate food allowance, i.e., fresh orange and whole wheat bread instead of orange juice and white bread.* Anderson, Lin, and Ward[7] have compiled dietary fiber information based on the new diabetic exchange list.[24] We do not recommend the addition of such items as unprocessed bran and cellulose to the diet. Such diets have been associated with decreased intestinal absorption of zinc, magnesium, calcium, and phosphorus,[65, 34] and in diets of marginal intake, these nutrients may become deficient.

CONCLUSION

Reluctance of physicians to take an aggressive posture toward dietary management of diabetes is not surprising, given the generally poor degree of patient compliance reported in the literature. West has defined several factors which contribute to this failure,[79] and a successful attempt at circumventing these obstacles in nonobese patients has been reported.[78] From the evidence cited here, however, it is apparent that a successful program of dietary intervention may provide substantial if not complete amelioration of metabolic abnormalities for the majority of diabetic patients. It is imperative, therefore, that more effective approaches to long-term compliance be developed, and that health professionals caring for diabetic patients have knowledge of the principles of dietary management as well as the most effective way to apply these principles.

*Editor's Comment - In order to obtain a diet with increased fiber content, we recommend the use of unrefined whole grains and breads and whole fruits and vegetables in lieu of highly processed foods which contain refined flours and starches; and a large proportion of simple carbohydrates (sugar, honey, corn syrups, etc.).

REFERENCES

1. ADA Special Report, Committee on Food and Nutrition. Principles of nutrition and dietary recommendations for patients with diabetes mellitus: 1971. Diabetes, 20:633, 1971.
2. Ahrens, E. H., Jr., Hirsch, J., Insull, W., et al.: The influence of dietary fats on serum lipid levels in man. Lancet, *1*:943, 1957.
3. Ahrens, E. H., Jr., Hirsch, J., Oette, K., et al.: Carbohydrate-induced and fat-induced lipemia. Trans. Assoc. Am. Physicians, 74:134, 1961.
4. Albrink, M. J.: Dietary and drug treatment of hyperlipidemia in diabetes. Diabetes, 23:913, 1974.
5. Albrink, M. J., and Meigs, J. W.: The relationship between serum triglycerides and skinfold thickness in obese subjects. Ann. N. Y. Acad. Sci., *131*:673, 1965.
6. Anderson, J. W.: Effect of carbohydrate restriction and high carbohydrate diets on men with chemical diabetes. Amer. J. Clin. Nutr., 30:402, 1977.
7. Anderson, J. W., Lin, W., and Ward, K.: Composition of foods commonly used in diets for persons with diabetes. Diabetes Care, *1*:293, 1978.
8. Antonis, A., and Bersohn, J.: The influence of diet on serum triglycerides in South African white and Bantu prisoners. Lancet, *1*:3, 1961.
9. Bagdade, J. D., Porte, D., Bierman, E. L.: Diabetic lipemia. A form of acquired fat-induced lipemia. New Engl. J. Med., 276:427, 1967.
10. Bar, R. S., Gorden, P., Roth, J., et al.: Fluctuations in the affinity and concentration of insulin receptors on circulating monocytes of obese patients. Effects of starvation, refeeding and dieting. J. Clin. Invest., 58:1124, 1976.

11. Bronte-Stewart, B., Antonis, A., Eales, L., et al.: Effects of feeding different fats on the serum cholesterol level. Lancet *1*:521, 1956.
12. Bierman, E. L., and Hamlin, J. T., III: The hyperlipemic effect of a low-fat, high-carbohydrate diet in diabetic subjects. Diabetes, *10*:432, 1961.
13. Bistrian, B. R., Blackburn, G. L., et al.: Nitrogen metabolism and insulin requirements in obese diabetic adults on a protein-sparing modified fast. Diabetes, 25:494, 1976.
14. Bistrian, B. R.: Recent developments in the treatment of obesity with particular reference to semistarvation ketogenic regimens. Diabetes Care, *1*:379, 1978.
15. Brodriff, A. J. M., and Humphreys, D. M.: Diverticular disease: three studies. Brit. Med. J., *1*:424, 1976.
16. Brunzell, J. D., Lerner, R. L., Hazzard, W. R., et al.: Improved glucose tolerance with high carbohydrate feeding in mild diabetes. New Engl. J. Med., *284*:521, 1971.
17. Brunzell, J. D., Lerner, R. L., Porte, D., Jr., et al.: Effect of a fat free, high carbohydrate diet on diabetic subjects with fasting hyperglycemia. Diabetes, 23:138, 1974.
18. Chait, A., Onitiri, A., Nicoll, A., et al.: Reduction of serum triglyceride levels by polyunsaturated fat — studies on the mode of action and on very low density lipoprotein composition. Atherosclerosis, 20:347, 1974.
19. Chiles, R., and Tzagournis, M.: Excessive insulin response to oral glucose in obesity and mild diabetes — study of 501 patients. Diabetes, *19*:458, 1970.
20. DeFronzo, R. A., Soman, V., Sherwin, R. S., et al.: Insulin binding to monocytes and insulin action in human obesity starvation, and refeeding. J. Clin. Invest., 62:204, 1978.
21. Drenick, E. J., Brickman, A. S., Gold, E. M.: Dissociation of the obesity-hyperinsulinism relationship following dietary restriction and hyperalimentation. Amer. J. Clin. Nutr., 25:746, 1972.
22. Eastwood, M. A.: Dietary fibre and serum lipids. Lancet, 2:1222, 1969.
23. Eastwood, M. A.: Perspectives on the bran hypothesis. Lancet, *1*:1029, 1974.
24. Exchange Lists for Meal Planning, New York, American Diabetes Association, and Chicago, American Dietetic Association, 1976.
25. Farquhar, J. W., Frank, A., Gross, R. C., et al.: Glucose, insulin and triglyceride responses to high and low carbohydrate diets in man. J. Clin. Invest., 45:1648, 1966.
26. Ginsberg, H., Olefsky, J. M., Kimmerling, G., et al.: Induction of hypertriglyceridemia by a low-fat diet. J. Clin. Endocr. Metab., 42:729, 1976.
27. Goulder, T. J., Alberti, K. G. M. M., Jenkins, D. J. A.: Effect of added fiber on glucose and metabolic responses to a mixed meal in normal and diabetic subjects. Diabetes Care, *1*:351, 1978.
28. Greenfield, M., Kolterman, O., Olefsky, J. M., et al.: The effect of ten days of fasting on various aspects of carbohydrate metabolism in obese diabetic subjects with significant fasting hyperglycemia. Metabolism, 27(Suppl. 2):1839, 1978.
29. Greenfield, M., Kolterman, O., Olefsky, J., et al.: An inquiry into the etiology of diabetic hypertriglyceridemia. Clin. Res., 27:44A, 1979.
30. Hadden, D. R., Montgomery, D. A. D., Skeely, R. J., et al.: Maturity onset diabetes mellitus: response to intensive dietary management. Brit. Med. J., 3:276, 1975.
31. Himsworth, H. P.: The dietetic factor determining the glucose tolerance and sensitivity to insulin of healthy men. Clin. Sci., 2:67, 1935–36.
32. Houtsmuller, A. J.: Fat and the treatment of diabetes mellitus. *In* Vergroesen, A. J., ed.: The Role of Fats in Human Nutrition. New York Academic Press, 1975, p.231.
33. Hulley, S. B., Burrows, M. J., Wilson, S., et al.: Lipid and lipoprotein responses of hypertriglyceridemic outpatients to a low-carbohydrate modification of the AHA fat controlled diet. Lancet, 2:551, 1972.
34. Ismail-Beigi, F., Reinhold, J. G., Faraji, B., et al.: Effects of cellulose added to diets of low and high fiber content upon the metabolism of calcium, magnesium, zinc and phosphorus by man. J. Nutr., *107*:510, 1977.
35. Jenkins, D. J. A., Leeds, A. R., Newton, C., et al.: Effects of pectin, guar gum and wheat fibre on serum cholesterol. Lancet, *1*:116, 1975.
36. Jenkins, D. J. A., Leeds, A. R., Goff, D. V., et al.: Unabsorbable carbohydrates and diabetes: decreased postprandial hyperglycaemia. Lancet, 2:172, 1976.
37. Jenkins, D. J. A., Leeds, A. R., Gassull, M. A., et al.: Decrease in postprandial insulin and glucose concentrations by guar and pectin. Ann. Intern. Med., *86*:20, 1977.
38. Jenkins, D. J. A., Wolever, T. M. S., Hockaday, T. D. R., et al.: Treatment of diabetes with guar gum. Lancet, 2:779, 1977.
39. Kaufmann, R. L., Assal, J. Ph., Soeldner, J. S., et al.: Plasma lipid levels in diabetic children. Effect of diet restricted in cholesterol and saturated fats. Diabetes, 24:672, 1975.
40. Keys, A., Grande, F., and Anderson, J. T.: Fiber and pectin in the diet and serum cholesterol concentration in man. Proc. Soc. Exper. Biol. Med., *106*:555, 1961.
41. Kiehm, T. G., Anderson, J. W., and Ward, K.: Beneficial effects of a high carbohydrate, high fiber diet on hyperglycemic diabetic men. Amer. J. Clin. Nutr., 29:895, 1976.

42. King, R. C., Dobree, J. H., Kok, D. A., et al.: Exudative diabetic retinopathy: spontaneous changes and effects of a corn oil diet. Brit. J. Ophthal., *47*:666, 1963.
43. Kinsell, L. W., Patridge, J., Boling, L., et al.: Dietary modification of serum cholesterol and phospholipid levels. J. Clin. Endocrinol. Metab., *12*:909, 1952.
44. Kinsell, L. W., Walker, G., Michaels, D., et al.: Dietary fats and the diabetic patient. New Engl. J. Med., *261*:431, 1959.
45. Kissebah, A. H., Adams, P. W., and Wynn, V.: Inter-relationship between insulin secretion and plasma free fatty acid and triglyceride transport kinetics in maturity onset diabetes and the effect of phenethylbiguanide (phenformin). Diabetologia, *10*:119, 1974.
46. Knittle, J. L., Ahrens, E. H. Jr.: Carbohydrate metabolism in two forms of hypertriglyceridemia. J. Clin. Invest., *43*:485, 1964.
47. Lees, R. S., Fredrickson, D. A.: Carbohydrate induction of hyperlipemia in normal man. Clin. Res., *13*:327, 1965.
48. Lenner, R. A.: Studies of glycemia and glycosuria in diabetics after breakfast meals of different composition. Amer. J. Clin. Nutr., *29*:716, 1976.
49. Miettinen, T. A.: Cholesterol production in obesity. Circulation, *44*:842, 1971.
50. Miranda, P. M., and Horwitz, D. L.: High fiber diets in the treatment of diabetes mellitus. Ann. Intern. Med., *88*:482, 1976.
51. Moser, C. R., and Anderson, J. W.: Improvement of postprandial triglyceride values in diabetes from high carbohydrate diets or improved diabetic control. Diabetes, 22:294, 1973.
52. Nestel, P. J., and Whyte, H. M.: Plasma free fatty acid and triglyceride turnover in obesity. Metabolism, *17*:1122, 1968.
53. Nestel, P. J., Whyte, H. M., and Goodman, D. S.: Distribution and turnover of cholesterol in humans. J. Clin. Invest., *48*:982, 1969.
54. Nikkilä, E. A., and Hormila, P.: Serum lipids and lipoproteins in insulin-treated diabetes. Demonstration of increased high density lipoprotein concentrations. Diabetes, 27:1078, 1978.
55. Olefsky, J., Reaven, G. M., and Farquhar, J. W.: Effects of weight reduction on obesity. Studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects. J. Clin. Invest., *53*:64, 1974.
56. Olefsky, J. M., Farquhar, J. W., and Reaven, G. M.: Reappraisal of the role of insulin in hypertriglyceridemia. Amer. J. Med., *57*:551, 1974.
57. Olefsky, J. M.: Decreased insulin binding to adipocytes and circulating monocytes from obese subjects. J. Clin. Invest., *57*:1165, 1976.
58. Patel, J. C., Metha, A. B., Dhirawani, J. K., et al.: High carbohydrate diet in the treatment of diabetes mellitus. Diabetologia, 5:243, 1969.
59. Pollack, H.: Fat content of the diabetic diet. Diabetes, *9*:145, 1960.
60. Rabinowitz, D., and Zierler, K. L.: Forearm metabolism in obesity and its response to intra-arterial insulin. J. Clin. Invest., *41*:2173, 1962.
61. Reaven, G. M., Lerner, R. L., Stern, M. P., et al.: Role of insulin in endogenous hypertriglyceridemia. J. Clin. Invest., *46*:1756, 1967.
62. Reaven, G., and Miller, R.: Study of the relationship between glucose and insulin responses to an oral glucose load in man. Diabetes, *17*:560, 1968.
63. Reaven, G. M., and Olefsky, J. M.: Increased plasma glucose and insulin reponses to high carbohydrate feedings in normal subjects. J. Clin. Endocrin. Metab., *38*:151, 1974.
64. Reaven, G. M., and Olefsky, J. M.: Role of insulin resistance in the pathogenesis of diabetes mellitus. Adv. in Metab. Disorders, *9*:313, 1978.
65. Reinhold, J. G., Farakji, B., Abadi, P., et al.: Decreased absorption of calcium, magnesium, zinc and phosphorus by humans due to increased fiber and phosphorus consumption as wheat bread. J. Nutr., *106*:493, 1976.
66. Santen, R. J., Willis, P. W., and Fajans, S. S.: Atherosclerosis in diabetes mellitus. Correlations with serum lipid levels, adiposity and serum insulin level. Arch. Intern. Med., *130*:833, 1972.
67. Savage, P. J., Dippe, S. E., Bennett, P. H., et al.: Hyperinsulinemia and hypoinsulinemia. Insulin responses to oral carbohydrate over a wide spectrum of glucose tolerance. Diabetes, *24*:362, 1975.
68. Schlierf, G., Reinheimer, W., and Stossberg, V.: Diurnal patterns of plasma triglycerides and free fatty acids in normal subjects and in patients with endogenous (type IV) hyperlipoproteinemia. Nutr. Metab., *13*:80, 1971.
69. Service, F. J., Molnar, G. D., Rosevear, J. W., et al.: Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes, *19*:644, 1970.
70. Sims, E. A., Horton, E. S., and Salans, L. B.: Inducible metabolic abnormalities during development of obesity. Ann. Rev. Med., 22:235, 1971.
71. Southgate, D. A. T., Bailey, B., Collinson, E., et al.: A guide to calculating intakes of dietary fiber. J. Hum. Nutr., *30*:303, 1976.

72. Stanik, S., and Marcus, R.: Insulin deficiency in obese patients with severe diabetes improves after weight loss. Clin. Res., 27:51A, 1979.
73. Stone, D. B., and Connor, W. D.: The prolonged effects of a low cholesterol, high carbohydrate diet upon the serum lipids in diabetic patients. Diabetes, *12*:127, 1963.
74. Trowell, H. C.: Dietary fiber hypothesis of the etiology of diabetes mellitus. Diabetes, 24:762, 1975.
75. Truswell, A. S., and Kay, R. M.: Absence of effect of bran on blood lipids. Lancet, 2:922, 1975.
76. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Part I. Design, methods and baseline characteristics. Diabetes, *19*(Suppl. 2), 1970.
77. Weinsier, R. L., Seeman, A., Herrera, M. G., et al.: High- and low-carbohydrate diets in diabetes mellitus. Study of effects on diabetic control, insulin secretion, and blood lipids. Ann. Intern. Med., *80*:332, 1974.
78. Weinsier, R. L., Seeman, A., Herrera, M. G., et al.: Diet therapy of diabetes. Description of a successful methodologic approach to gaining diet adherence. Diabetes, 23:669, 1974.
79. West, K. M.: Diet therapy of diabetes: an analysis of failure. Ann. Intern. Med., 79:425, 1973.
80. Yang, M.-U., and Van Itallie, T. B.: Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. J. Clin. Invest., *58*:722, 1976.

Stanford Medical Center
Stanford, California 94305

Nutritional Management of Chronic Renal Disease

*Malcolm A. Holliday, M.D.,**
*Kathryn McHenry-Richardson, M.S., M.P.H.,***
*and Anthony Portale, M.D.****

Nutrition therapy in renal disease is based on two concepts. The first is that as the renal capacity for excreting dietary excess and metabolic by-products diminishes, the dietary intake of certain nutrients must be limited. The second concept is that renal failure itself may lead to deficiencies of certain nutrients. This may be the result of decreased intake because of anorexia or dietary restriction, decreased absorption, excessive loss in the urine or during dialysis, or impaired production or metabolism by the diseased kidney. Diet supplementation is required when this occurs.

Viewed from the perspective of the individual with normal kidney function, the kidney is a regulatory organ that allows for variation in dietary intake by effecting corresponding alterations in excretion so that changes in intake result in neither deficiency nor excess. In health, the range of tolerance for intake of six macronutrients is wide (Table 1); as function declines, the limits of tolerance contract.[7,8] Absolute limits for patients with impaired renal function have not been defined but in general parallel the decline in glomerular filtration rate.

The kidney has endocrine as well as regulatory roles. Erythropoietin and 1,25-$(OH)_2$ vitamin D_3 are synthesized in the kidney, and decreased synthesis of these hormones leads to an abnormality in red cell production and mineral metabolism. Production of renin by the kidney may be affected, resulting in impaired sodium or acid base balance or blood pressure control.

An alteration in the metabolism of certain nutrients such as pyridoxine may accompany renal insufficiency. The requirement for pyridoxine is greater than the Recommended Dietary Allowance because

*Professor of Pediatrics, and Chief, Pediatric Nephrology, University of California, San Francisco, California
**Nutritionist, Pediatric Nephrology, University of California, San Francisco
***Fellow, Pediatric Nephrology, University of California, San Francisco

The nutrition program of the Children's Renal Center, University of California, San Francisco Medical Center, receives support from the State of California, Department of Health Services, Chronic Disease Control Section, Contract #78–62130.

Table 1. *Daily Average Intake and Minimum and Maximum Tolerances For Major Dietary Constituents For a 70 kg Adult Male – Average Values for Sedentary Living*

CONSTITUENT	AVERAGE	MINIMUM	MAXIMUM	RATIO
Calories	2,300	2,000	5,000	1:2.5
Protein (gm)	100	30	300	1:10
Potassium (mEq)	70	10	500	1:100
Hydrogen (mEq)	70	−100	300	–
Phosphorus (mg)	1,500	500	4,500	1:9
Sodium (mEq)	180	2	1,000	1:500
Water (ml)	2,000	750	15,000	1:20

of an alteration in the metabolism of pyridoxal phosphate, the active coenzyme form of the vitamin.

While metabolic alterations may develop with any significant reduction in renal function, clinical evidence for nutritional disturbance in adults is seldom evident until clearance values are 25 per cent of normal.[5] In children, a decrease in growth velocity may occur when the glomerular filtration rate falls to less than 50 per cent of normal, and signs of malnutrition may follow further reductions.[7] The term renal insufficiency seems appropriate for these states. Uremia is the best designation for patients who develop symptoms related to nitrogen retention.[64] This occurs with clearance values between 5 and 15 per cent of normal in adults and often at somewhat higher relative clearance levels in children.[40] End-stage renal disease is the term used to designate patients who require dialysis or transplantation.

The goal of nutritional management in renal insufficiency is to provide a diet that meets minimum requirements for health but does not exceed the tolerance limits of those nutrients whose absorption or excretion is affected by the decrease in renal function.[40, 78] In practice, nutritional therapy is limited by uncertainties regarding requirements and tolerances, by the degree to which patients accept dietary modification and by difficulties in providing a diet that meets requirements for some nutrients while not exceeding tolerance of others. In this discussion we will briefly review the basic principles for monitoring and modifying the intake of the most important nutrients. Practical considerations in applying these principles will be also presented.

Recommendations for nutritional requirements in health are presented in the Recommended Dietary Allowance manual.[58] While they may not be suited to patients with renal disease, they provide a good reference point.

ENERGY

In health, energy intake is governed in part by appetite which in turn is sensitive to energy expenditure. With a severe reduction in en-

ergy intake, basal metabolic rate declines and physical activity is reduced in an attempt to reduce energy expenditure. When intake is consistently less than expenditure, energy deficiency malnutrition develops, a clinical state characterized by a reduction in physical activity and diminished fat and muscle mass.[46]

Some patients with renal insufficiency, including those on dialysis, have reduced body fat and muscle mass[18] and have energy intakes which are less than 75 per cent of the Recommended Dietary Allowance (RDA).[49]* When such conditions exist, a presumptive diagnosis of energy malnutrition can be made.

The prevalence of energy malnutrition in uremia is not well documented. In non-dialyzed patients maintained on amino acid or keto acid supplements, energy intakes of 30 to 35 kcal/kg/day (70 to 80 per cent RDA) were reported.[30, 81] In a recent study of unsupplemented adults, energy intake measured during a one-week period was 33 kcal/kg/day; however, no significant correlation between energy intake and skinfold thickness or mean arm circumference was found.[18] Kopple[49] reported that 25 per cent of patients on dialysis have energy intakes less than 75 per cent of the RDA. He has summarized the experiences in adults and concluded that patients receiving 35 kcal/kg/day maintain a body weight which is stable but less than normal for adults of the same age.†

Other changes in body composition have been reported by Letteri and colleagues,[53] who found that 11 out of 35 adult patients on dialysis had low total body potassium values when compared with appropriate controls, reflecting diminished muscle mass; patients with renal insufficiency did not have low total body potassium. Coles[18] found that intracellular water and skinfold thickness were reduced in patients with renal insufficiency.

The prevalence of energy malnutrition appears to be greater in children. The energy requirement per kilogram of body weight is higher than in adults because of differences in body composition and activity levels (Table 2). Energy requirements are also greater in relation to energy reserves, making children more susceptible to the rapid development of energy deficiency.[38]

West and Smith[83] reported that food intake was inadequate in a high percentage of children with renal disease and growth retardation. We have found energy intake to be low in most children on dialysis;[67] it is also low in many children with renal insufficiency.[5] Similar findings have been reported by others.[10, 15] A low weight for height ratio,[74] decreased intracellular water,[39] low total body potassium,[82] and reduced skinfold thickness (McHenry-Richardson, unpublished obser-

*The use of 75 per cent RDA as indicative of inadequate energy intake is based on the relationship of the RDA to maintenance energy requirements. Maintenance energy requirement is a term used to define energy needed to maintain body composition with an allowance for activity. It is estimated to be 1.5 × basal metabolic rate which is equal to 65 to 75 per cent RDA.[74] For that reason an intake of less than 75 per cent of RDA may result in changes in body composition, i.e., loss of fat and muscle mass.

†Extracellular fluid volume is greater in patients with renal insufficiency; thus weight corrected to normal ECF would be further reduced.[41] For this reason, the use of body weight as an index of nutritional status may be inaccurate.

Table 2. *Recommended Dietary Allowances (1974) by Weight*

AGE		ENERGY (KCal)/kg	PROTEIN (gm)/kg
INFANT			
0 – 6 mos (–6 kg)		117	2.2
6 mos–12 mos (6–9 kg)		108	2.0
CHILDREN			
1–3	(13–19 kg)	100	1.8
4–6	(20–29 kg)	90	1.5
7–10	(30–43 kg)	80	1.2
ADOLESCENTS			
11–14	(44–60	54–64	1
15–18	61–66)	39–49	0.9
ADULTS			
18 Female		31 35	0.8
Male		34–44	0.8

vation) are common in children with renal failure, particularly in those on dialysis. Energy intake correlates with growth velocity in children in some studies[10, 67] but not in others.[8, 10]

The major cause of energy deficiency in patients with uremia is inadequate appetite or anorexia. The possible reasons for anorexia are many and include malaise, headache, post dialysis fatigue or nausea, altered taste perception, and mental depression. Dietary restriction often excludes favorite foods; drug therapy may depress appetite.

Efforts to supplement energy intake should be undertaken within the framework of careful nutritional management and assessment of nutritional status. This assessment should include:

1. Evaluation of dietary intake
   a. Current eating habits (of the patient and family) including dietary restrictions
   b. Analysis of the patient's diet records for energy, protein (including per cent high biological value), vitamins, calcium, phosphorus, sodium, potassium, and other minerals such as iron, zinc, copper, and iodine. Computer analysis provides easy access to this information (Table 3).*
2. Anthropometric measurements
   a. Height relative to age[59] expressed as standard deviation score for mean for that age.[61]
   b. Weight for height ratio
   c. Mean arm circumference
   d. Triceps skinfold thickness and subscapular skinfold thickness

*UCSF Clinical Nutrient Report: Pediatric Nephrology. Computer program was developed in cooperation with the State of California, Department of Health Services, Chronic Disease Control Section. Nutrient information is derived from: Pennington, J. A.: Dietary Nutrient Guide, AVI Publishing Co., Westport, Connecticut, 1976.

Table 3. *State of California Department of Health UCSF Clinical Nutrient Report: Pediatric Nephrology*

Date: 11/02/78 ID No: 33 Physician: Dr. Portale
Patient: Institution: UCSF
Ht: 125.0 cm Wt: 22.0 kg Ht Age: 8 yr, 0 mo
Sex: F B.D.: 6-6-66 Chrono Age: 12 yr, 0 mo

Comments
and Diagnosis

Menu Start Date: 9-13-78 No. Menus Analyzed: 2

TOTAL DAILY NUTRIENTS INGESTED

MACRO		%RDA
KCAL	1203.1	50
KJ	4085.9	
PRO	42.8	119
N2-T	6.7	

GENERAL (G)	
CHO-T	104.4
CHO-F	0.4
SUCR	8.6
FAT	68.1
SFA	26.5
PUFA	24.6
CHOLE	0.1
ASH	7.8
H_2O	852.0

VITAMINS		%RDA
A (IU)	1302.0	39
D	246.0	61
E	0.8	13
C (MG)	103.5	259
THIA	0.5	48
RIBO	1.3	111
NIACIN	5.9	37
B6 (UG)	662.7	55
B12	3.8	193
BIOTIN	33.3	
FOLIC	73.0	24
PANTO	2971.9	
K1	21.0	

AMINO ACIDS (MG)	
ISO	2353.8
LEU	3608.5
LYS	3342.7
MET	935.7
PHE	1837.9
THR	1767.5
TRY	508.5
VAL	2472.7
ARG	2208.6
CYS	465.4
HIS	1149.2
TYR	1812.8
AAREM	20393.7

MINERALS (MG)		
CA	745.3	93
P	783.3	98
NA	1632.1	
K	1861.1	
MG	127.0	51
ZN	5.7	57
CU	0.5	
FE	3.8	38
I (UG)	55.0	50
EAA-T	16827.75	
RATIO	0.65	

% KCAL Contribution:	14 PRO	35 CHO	51 FAT
Formula Intake:	0 KCAL-T	0 % KCAL	0 % PRO
MEQ Electrolytes:	37.3 CA	71.0 NA	47.7 K
CA:P Ratio:	0.952		

3. Biochemical
   a. Serum electrolytes, including calcium and phosphorus, blood urea nitrogen, creatinine
   b. Serum albumin, transferrin
   c. Cholesterol, triglycerides
   d. Serum iron, red blood cell folate level
4. Evaluation of patient's knowledge of nutrition as it applies to therapeutic diet.
5. Special considerations such as allergies, cooking facilities, physical disabilities, language barrier and economic restrictions which may interfere with patient cooperation.

Dietary manipulations designed to increase caloric intake are achieved by many devices. The addition of sauces, gravies, cream, mayonnaise or butter to meats, vegetables, and pasta; flavored carbohydrate powders and syrups to milk; jam, jelly, honey, or sweet sauces to fruit or vegetables; and frosting to cakes or cookies will increase calorie density of the diet. Carbohydrate polymers (Polycose, Controlyte and Caloreen) can be incorporated into the usual foods or can be used in making special food items such as high-calorie desserts or beverages. Whipping cream or emulsified vegetable oils can also be used. The use of these supplements has resulted in improved intake and growth and has heightened the sense of well-being in some but not in all instances. Preventive dental care must accompany the use of carbohydrate supplements since the addition of sticky sweets to the diet may cause dental caries.

Uremic patients including children[25, 43] frequently have hypertriglyceridemia. Since carbohydrate supplements may raise plasma triglyceride levels further,[63] the use of emulsified vegetable oils may prove to be the best caloric supplement.

Efforts to improve presentation of food as well as its content are important, e.g., picnics, parties, and cooking sessions all provide a pleasant setting for eating. Nagging depresses appetite.

Recommendations

Recommendations for energy intake in both adults and children with renal insufficiency and on dialysis are commonly based on the Recommended Dietary Allowances (RDA–1974) with adjustments for body size and activity level.[58] The RDA is proposed as an "average and approximate allowance for feeding groups" and the RDA for energy was established as the lowest value thought to be supportive of the health of the average person. The RDA were not designed to provide recommendations for nutrient intake of individuals with special needs because of infection, metabolic disorders, or chronic illness. Thus while the RDA may be used as a guideline, more appropriate recommendations for individual patients must be developed from observation of appetite, activity level, growth and weight gain.

ADULTS. RDA for sex and age (see Table 2) with appropriate adjustments discussed above.

CHILDREN. Renal insufficiency and dialysis: RDA for sex and height with appropriate adjustments discussed above.

PROTEIN

In Western societies the average dietary protein intake of healthy adults is 1.7 gm/kg/day which is more than twice the RDA (0.8 gm/kg/day).

Patients with symptoms of uremia who are ingesting high-protein diets become less symptomatic when the intake of dietary protein is lowered. Impressive results were reported by Giovannetti and Maggiore[31] who found improvement in patients given 20 gm of high biological value protein. Kopple and Coburn[30] in a comparative study of patients with advanced renal insufficiency, found a 40 gm protein diet (0.6 gm/kg/day) superior to a 20 gm protein diet in relieving symptoms of uremia, while a 70 gm (1 gm/kg/day) diet caused an increase in symptoms. This study highlights the constraints that uremia imposes on the intake of dietary protein; while adequate protein must be supplied, the amount commonly contained in normal diets may provide too much.

Diets low in protein and energy have resulted in protein energy malnutrition in uremic patients. Despite relief of uremic symptoms, negative nitrogen balance occurs,[49] adipose tissue and muscle mass are lost, and plasma protein values are low (albumin, C_3, complement, and transferrin). Negative nitrogen balance occurs when low-protein diets are used, despite relief of uremic symptoms.[49] Dietary energy[4] and protein[29] correlate positively with nitrogen balance.

Low protein diets supplemented with essential amino acids have improved the clinical status of patients with advanced renal insufficiency (GFR 5 per cent normal).[30] Similar diets supplemented with three amino acids and ketoanalogues of five other amino acids have likewise led to clinical improvement in such patients.[7] However, supplements of either essential amino acids or ketoanalogues have no demonstrable nutritional effect when they were used in conjunction with diets providing more than 0.4 gm protein/kg/day.[11]

Recommendation

ADULTS. For patients with renal insufficiency, uremic symptoms can be lessened and the initiation of dialysis therapy delayed by restricting the intake of dietary protein. The best evidence suggests an intake of 0.6 gm/kg/day of high biological value protein (40 gm in the 70 kg adult). A recommendation less than RDA for normals is justified because excess protein is potentially toxic in uremia. When dialysis becomes necessary, protein intake should be increased to allow for the loss of amino acids that occurs during dialysis. One gm kg/day of high biological value protein is recommended for patients on dialysis.

CHILDREN. The protein requirement per kilogram body weight, similar to the energy requirement, is higher in children than in adults (Table 2). The requirement for infants up to 1 year of age is increased because of the rapid growth rate during this period. After 1 year of age, the higher requirement may be related to higher basal energy expenditure or higher rate of protein turnover. Protein requirements, particu-

larly for essential amino acids, also are higher relative to muscle mass so that the consequences of inadequate protein intake appear rapidly.[27, 58]

The recommendation for children with renal insufficiency is that of the RDA (see Table 2). For children over 2 years of age who are on hemodialysis or peritoneal dialysis, a diet which provides 1.5 to 2.0 gm/kg/day of high biological value protein should be sufficient to prevent negative nitrogen balance as long as energy intake is adequate. Dietary proteins derived from animal sources (egg, milk, meat, fish) are of the highest biological value. The addition of commercially prepared low protein grain and bread products may make these dietary changes easier, but diets containing lower quality protein (primarily vegetable and grain), combined with supplements of amino acids may be more palatable and also beneficial.[30] Higher protein intakes than those recommended may have undesirable consequences similar to those observed in nondialyzed uremic patients.

Some children on dialysis have become severely malnourished and intolerant to food. Parenteral nutrition therapy and gastrostomy feedings have improved their clinical and nutritional status.[1] Guidelines for the use of oral supplements of essential amino acids or ketoanalogues in dialysis patients have not been developed.

CALCIUM AND PHOSPHORUS

The RDA for calcium is 800 mg in adults, 500 to 1000 mg in children up to 11 years and 1200 mg in adolescents. The diets of patients with renal insufficiency and those on dialysis frequently do not satisfy this requirement. Calcium absorption from the gastrointestinal tract is under control of several factors which impair calcium absorption in renal insufficiency; important among these is the renal hormone 1,25-dihydroxy vitamin D_3.[34]

With progressive loss of renal function, retention of dietary phosphorus occurs because of diminished excretion. It has been proposed that transient elevations in serum phosphate concentration cause a reciprocal fall in calcium concentration which stimulates the secretion of parathyroid hormone.[69] Phosphorus excretion is augmented by the action of parathyroid hormone on the renal tubule and homeostasis is restored, but at the expense of parathyroid hormone overactivity.[9] The hyperparathyroidism of renal insufficiency both has been prevented[70] and reversed[45] in dogs by restricting the intake of phosphorus in proportion to the reduction in renal function.

Control of dietary phosphorus intake and administration of phosphate binding gels is generally instituted when the serum phosphate concentration becomes elevated. Restriction of phosphorus intake in early renal insufficiency may be of value, especially in growing children, in preventing the development of renal osteodystrophy; however, the risk of bone disease as a result of phosphate depletion must be born in mind.[47]

Phosphorus is present in many foods, particularly processed foods

and efforts to reduce dietary intake include restriction of meat, milk, legumes, and carbonated beverages. Dietary restriction may be difficult because it excludes commonly used foods. Usually phosphate binding gels are used in preference to low phosphorus diets. Incorporation of the powdered gel into cookies or fudge provides an acceptable method of administration.

Recommendation

The goal of management is the achievement of normal levels of serum calcium and phosphorus, reduction of hyperparathyroidism, and restoration of normal vitamin D activity. Aluminum hydroxide is used to bind phosphorus; the dose varies with the size of the patient, the dietary intake of phosphorus and the level of renal function. Oral calcium supplementation with 1 to 2 gm of elemental calcium per day can be achieved by the use of calcium carbonate (40 per cent calcium) or calcium gluconate (Neo-Calglucon, 6.4 per cent calcium).

Vitamin D_2 (calciferol), D_3 (cholecalciferol), and dihydrotachysterol (DHT) have been used successfully to treat renal osteodystrophy. The active metabolites of vitamin D, 25-OH-D_3 and 1,25-$(OH)_2D_3$ and 1-α OH-D_3, a synthetic analogue of 1,25-$(OH)_2D_3$, are now available for use. Guidelines regarding the choice of the best drug, appropriate dosage and optimal time to begin using such compounds must await further clinical investigation.

SODIUM

The minimum requirement for sodium in the normal adult is very low, less than 250 mg (about 10 mEq) per day; the maximal tolerance is high, up to 25 gm (1000 mEq) per day.[2] The requirement for children is higher and the maximal tolerance lower than in adults.[19]

As renal function declines, most patients remain in sodium balance, but their ability to tolerate severe restriction or marked excess in sodium intake is diminished. In one study of patients with a mean creatinine clearance of 10 ml per minute, a sodium intake of 1000 mg (40 mEq) per day resulted in a negative sodium balance. On an intake of 4 gm (180 mEq) of sodium per day, a slightly positive balance occurred.[71] This range is considerably less than that tolerated by normal individuals (10 to 1000 mEq). While patients with advanced renal disease have difficulty conserving sodium during acute restriction of dietary sodium,[17] Bricker and colleagues[23] demonstrated that patients could slowly adapt to very low levels of sodium intake.

Some patients with renal insufficiency particularly those with medullary cystic disease have a specific defect which causes them to lose excessive amounts of sodium in the urine. Without supplemental sodium, the extracellular fluid volume contracts, the glomerular filtration rate is decreased, and the patients suffer the clinical consequences of these changes, i.e., fatigue and increasing uremia. In instances in which the defect is severe, shock and dehydration may

result, often associated with hyponatremia. Milder examples may be quite subtle. Such cases can only be detected when patients are given supplementary salt and improvement is noted, i.e., fatigue disappears, and the degree of uremia is decreased.

As patients become oliguric or anuric and require dialysis the only means for removing dietary sodium is ultrafiltration during dialysis. Generally, patients ingest fluids during the interdialytic period in proportion to their sodium intake, and the resulting expansion of the ECF volume is isotonic. If sodium concentration in serum remains in the normal range, interdialytic weight gain is a relatively accurate measure of sodium intake: i.e., a weight gain of 1 kg is equivalent to an ECF expansion of 1 liter, and a sodium intake of 130 to 140 mEq. The removal of ECF volume by ultrafiltration should match the weight gain between dialyses if ECF volume is to remain stable. Those patients who ingest large quantities of salt in the interdialytic period may not tolerate removal of the excessive ECF volume at dialysis. Such patients have a chronic overexpansion of the ECF volume and are often hypertensive. When this occurs, more stringent dietary restriction of salt may be very useful in controlling the excessive weight gain between dialyses.

The maximum tolerance for sodium is related to body weight. A child's energy intake per kilogram of body weight is approximately twice that of an adult and a diet of comparable composition would provide twice the sodium chloride content per kilogram.[8] Thus, a sodium burden twice that of an adult is imposed on the child without kidney function who eats the same diet as an adult. Restriction of sodium in children must be more severe to achieve the same relative level of salt intake while meeting energy needs.

Recommendation

ADULTS WITH RENAL INSUFFICIENCY AND ON DIALYSIS. Sodium restriction of 2.0 to 2.5 gm day (87 to 109 mEq) is recommended in patients who are hypertensive or edematous or to control interdialytic weight gain.

CHILDREN WITH RENAL INSUFFICIENCY (NON-SALT WASTING) AND ON DIALYSIS. Sodium restriction to at least 50 mg kg day (2.0 to 3.0 mEq kg day) is recommended in patients with hypertension or edema or with excessive interdialytic weight gain.

The amount of sodium provided by the average American diet is 4.0 gm (180 mEq) per day.[9] Even mild sodium restriction requires that food regularly consumed by the United States population be eliminated from the diet. Commercially prepared fried chicken, pizza, and canned tomato soup have excessive salt, whereas these same items are acceptable if prepared without adding salt. Encouraging patients to prepare meals from fresh unprocessed foods rather than highly salted prepared foods results in a diet which has a more appropriate salt content and may be more nutritious as well. When diet modifications are accepted by a patient and family, dietary sodium intake can be reduced to 1.5 to 2.0 gm (65 to 87 mEq) per day.

POTASSIUM

The minimum requirement for potassium in the normal individual is easily met by any diet that meets energy and protein requirements. The capacity to excrete large quantities of potassium is considerable (500 mEq/day). As renal function declines, there is an increase in potassium excretion per nephron[89] so that intakes of 100 to 200 mEq of potassium per day are tolerated until clearance values become less than 10 per cent of normal. As a consequence, dietary control of potassium may not be necessary until the patient requires dialysis.

Patients on dialysis who are anuric retain excess dietary potassium during the interdialytic period. Since uremia lowers the cellular uptake of a potassium load,[90] it seems likely that the removal of potassium during dialysis results in some reduction in cell potassium so that at the end of dialysis, concentration is below normal. During the interdialytic period, this cycle is reversed as dietary intake leads to potassium retention. Potassium concentration in muscle in excess of normal has not been reported in anuric patients.[91] When potassium intake exceeds all capacity for uptake, hyperkalemia results and restriction of potassium intake and administration of a potassium binding agent (Kayexalate) becomes necessary. Cell potassium concentration and total body potassium are normal or reduced in patients with uremia, including those on dialysis.[92-94] The dietary changes necessary to reduce potassium intake include the restriction of most fruits and vegetables. Elimination of fruits and vegetables from the diet introduces problems of diet palatability and potential vitamin deficiencies, so that in many patients, moderate potassium restriction combined with administration of a potassium-binding resin provides control of serum potassium concentration. The resin can be taken with juice or Kool-Aid or incorporated into a chocolate fudge without significantly limiting its capacity to bind potassium. If dosage and medication schedule are adapted to the individual, the fudge can also serve as the vehicle for phosphate-binding gels, eliminating the need for additional capsules.

Recommendations

Restriction of dietary potassium and administration of potassium binding agents is recommended when decreasing renal function results in hyperkalemia. Severity of dietary restriction is dependent on serum potassium levels, concurrent use of potassium binder (Kayexalate), and nutritional considerations of nutrient adequacy and diet palatability.

VITAMINS

Inadequate dietary intake of vitamins is common in patients with renal failure, in part because of anorexia, dietary restriction of protein, potassium and phosphorus, and the use of energy and protein supplements which do not contain vitamins. Analysis of 16 food records from

11 children with renal insufficiency not on dialysis revealed that the intake of vitamin A, folacin, and ascorbic acid was less than 68 per cent of RDA for height and age in more than half the records. This occurred despite the fact that the intake of protein and calories was adequate and nutrient intake had been supplemented with vitamin D, calcium, iron, and B vitamins (McHenry-Richardson, unpublished observations).

In patients with renal insufficiency, recommendations for vitamin supplementation include the use of daily multivitamin preparation (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, and biotin); in dialysis patients, additional supplementation of folic acid, ascorbic acid, and pyridoxine is recommended (see below).

FOLACIN

Dialysis patients are susceptible to folate deficiency for several reasons, including poor dietary intake, destruction of the vitamin during food preparation, and losses during dialysis. Low plasma and serum folacin levels have been reported in patients on hemodialysis[33, 52, 54] and those on peritoneal dialysis,[52] although other investigators have found plasma[84] and red blood cell folate levels[54, 84] to be normal. Clinical evidence of folic acid deficiency has been reported in some studies[33, 65] but not in others.[54, 84] Hypersegmentation of polymorphonuclear leukocytes, megaloblastic erythropoiesis and myelopoiesis in bone marrow were observed in hemodialysis patients and a decrease in segmentation was observed when folate was administered.

Inhibition of membrane transport of folate in uremia is related to an inhibitory effect of anions, particularly phosphate, the plasma level of which is usually high in uremic patients.[44] This inhibitory effect decreases the rate of uptake of folate into folate-dependent cells and contributes to marginal folate status.

Absorption of folate is reported to be normal in patients on hemodialysis,[26] although it may be decreased in the presence of zinc deficiency.[79] Dietary intake of folate often is not sufficient to meet nutrient requirements and to replace dialysis losses, estimated to be between 9 and 32 μg per dialysis session.[36]

While folacin is found in many foods and the best sources are yeast, organ meats, leafy green vegetables, and some fresh fruits, the intake of these foods may be restricted in uremic patients. Folate also is highly susceptible to oxidative destruction and cooking methods recommended for potassium leaching, such as extended soaking and boiling, may destroy the folate content of foods. Cooking, canning, and refining destroys between 50 and 95 per cent of the folate content of foods.[37]

The recommendation for folate supplementation of dialysis patients by the Food and Drug Administration was changed in 1971 from 5 mg per day to 1 mg per day.[28] More recent research suggests that the administration of 1 mg of folate following dialysis in adult patients is

sufficient to maintain normal serum folate levels and to provide adequate folacin for maintenance of normal erythropoiesis.[68]

Recommendation

Dialysis Patients, Adults and Children: 1 mg Following Dialysis. Red blood cell folate levels should be monitored to insure that this amount is adequate to maintain normal body content of folate.[13]

ASCORBIC ACID

The inadequate intake of ascorbic acid in hemodialysis patients, caused by the restriction of potassium-rich fruits and vegetables, and losses of ascorbic acid during hemodialysis may explain the low plasma and leukocyte ascorbic acid levels reported in this group of patients.[76] Supplementation of ascorbic acid is necessary.

Recommendation

Fifty to 100 mg per day in pediatric and adult dialysis patients.

PYRIDOXINE — VITAMIN B_6

There is evidence to suggest that the metabolism of pyridoxine is altered in uremia. Low plasma and red blood cell pyridoxine levels[24, 51] and reduced plasma levels of pyridoxal phosphate,[75] the coenzyme form of the vitamin, are reported in dialysis patients. Elevated index on the enzyme stimulation test (erythrocyte glutamic-pyruvic transaminase) is also suggestive of pyridoxine deficiency and of increased dietary requirements for the vitamin in patients with renal disease.[51]

Vitamin B_6 occurs in a wide variety of foods in the form of pyridoxine, pyridoxal, and pyridoxamine, all of which are converted to the coenzyme pyridoxal phosphate (PLP). PLP is active in numerous enzyme systems primarily those associated with nitrogen metabolism, although phosphorylase, the enzyme required for the breakdown of glycogen to glucose-1-phosphate, is also PLP dependent. The importance of PLP in these enzyme systems may explain the variety of clinical signs present in B_6 deficiency[6, 12, 22] some of which are also present in uremia. Depression of the immune response, common to both uremia and pyridoxine deficiency, has been shown in patients on dialysis to be responsive to administration of pyridoxine.[24] The normalization of biochemical indices of pyridoxine deficiency in dialysis patients was achieved by administration of 5 mg of pyridoxine hydrochloride per day[77] which also suggests that the requirement for the vitamin is increased in uremia. Although the etiology of pyridoxine deficiency in uremia has not been determined, the presence of circulating competitive inhibitors,[63] increased metabolic clearance of PLP,[71] and impaired absorption during administration of hydralazine[60] have been reported. The requirement for pyridoxine in uremic children has not been determined.

Recommendation

1.2 to 2.0 mg. pyridoxine per day for adults and children; 5.0 mg/day may be given safely to assure avoidance of pyridoxine deficiency.

TRACE MINERALS

Trace minerals may become deficient in patients with uremia due to altered metabolism, inadequate dietary intake, losses during dialysis and increased excretion.

IRON

Iron deficiency may occur in patients with renal insufficiency as a result of inadequate intakes of iron and copper. Bleeding abnormalities associated with platelet defects may increase menstrual blood loss in females. Blood losses during dialysis and frequent laboratory tests deplete iron stores and increase the dietary requirement for iron.

The presence of iron deficiency can be identified by: (1) Plasma iron levels less than 40 μg/100 ml. (2) Serum transferrin or iron-binding capacity greater than 350 μg/100 ml. (3) Transferrin saturation less than 16 per cent. The level of serum transferrin can be lower in the presence of infection and malnutrition, and iron deficiency may be masked.

Recommendation

In patients with chronic blood loss and those with renal insufficiency whose dietary intake of iron is less than 68 per cent of the RDA, an effort should be made to include iron-rich foods in the diet to prevent iron deficiency. In patients with the diagnosis of iron deficiency, 600 mg of ferrous sulfate in daily divided doses is recommended in addition to the inclusion of iron-rich foods in the diet. Provision of adequate ascorbic acid will increase absorption of both dietary iron and supplemental iron.[57]

ZINC

Reduced dietary intake of zinc, in part due to dietary restriction of protein, may result in zinc deficiency. Low plasma zinc levels have been reported in adults on chronic hemodialysis[20, 55] and in nondialyzed uremic children.[32] Other investigators have reported normal RBC zinc levels in hemodialysis patients,[55] normal concentrations of zinc in hair, muscle,[20, 36, 55, 56, 62] heart, liver and testes, and decreased levels in the kidney of uremic rats.[20]

It has not been determined whether low plasma zinc levels in uremia reflect actual zinc deficiency or are due to redistribution of zinc in

body pools or to a change in the binding of zinc to plasma proteins. In clinical trials, zinc supplementation has been effective in ameliorating uremic symptoms of hypogeusia and anorexia,[3] and preliminary reports suggest that zinc supplementation is beneficial in treating male impotence associated with uremia and chronic dialysis.[2]

Reports of enhanced zinc absorption and zinc uptake into bone during periods of vitamin D_3 supplementation in rats[1] suggest that the requirement for zinc is increased during periods of calcification and skeletal growth. Other research suggests that the effect of vitamin D on zinc metabolism is independent of calcification and bone growth.[11] In either case, the treatment of renal osteodystrophy in uremic patients, especially children, may have important effects on zinc status.

Recommendation

We recommend that an adequate intake of zinc be insured either by supplementation or by inclusion of zinc-rich foods in the diet (oysters, crab, organ, and other meats). The intake of zinc considered to be adequate for patients with renal insufficiency is that recommended by the RDA.[58]

COPPER

A dietary intake of copper less than the required amount[58] has been observed in children on hemodialysis (McHenry-Richardson, unpublished observations). Copper depletion as evidenced by low levels of copper in serum, skin, kidney, adipose tissue, and muscle was reported in nondialyzed uremic children.[32] Supplementation of copper or intake of copper-rich foods (nuts, shellfish, organ meats, raisins and legumes) is recommended to prevent copper deficiency.

SUMMARY

The importance of nutritional evaluation and diet therapy in the overall management of the patient with chronic renal disease is unquestioned. Its application often is limited by a lack of knowledge regarding the requirement for certain nutrients in health as well as the way in which these requirements are modified by chronic disease. However, the most important and often the most difficult task is engaging the cooperation of the patient in the nutritional management of his disease. Acceptance of dietary manipulation depends upon the patient's family structure and the importance of food and mealtime within the particular cultural and ethnic background. Dietary recommendations implemented by the parents of pediatric patients may produce untoward changes in the child's behavior, attitudes toward food, or relationships with other family members. Dietary recommendations must be carefully planned and their effect reevaluated. They should be individualized to the age, intellectual skills, and developmental stage of the patient.

REFERENCES

1. Abitol, C. L., and Holliday, M. A.: Total parenteral nutrition in anuric children. Pediatr. Res., *10*:351, 1976.
2. Antonious, L. D., and Shalhoub, R. J.: Zinc in the treatment of chronic renal failure. Dialysis and Transplantation, 7:912, 1978.
3. Atkin-Thor, E., Goddard, B. W., O'Nion, J., et al.: Hypogeusia and zinc depletion in chronic dialysis patients. Am. J. Clin. Nutr., *31*:1948, 1978.
4. Becker, W. M., and Hoekstra, W. G.: Effect of vitamin D on ^{65}Zn absorption, distribution and turnover in rats. J. Nutr., *90*:301, 1966.
5. Berlyne, G. M., and Hocken, A. G.: The dietary treatment of chronic renal failure. *In* Berlyne, G. M., ed.: Nutrition in Renal Disease. Baltimore, Williams and Wilkins, 1968.
6. Bessey, O. A., Adam, D. J., and Hansen, A. E.: Intake of vitamin B_6 and infantile convulsions: A first approximation of requirements of pyridoxine in infants. Pediatrics, *20*:33, 1957.
7. Betts, P. R., and Magrath, G.: Growth pattern and dietary intake of children with chronic renal insufficiency. Brit. Med. J., 2:189, 1974.
8. Betts, P. R., Magrath, G., and White, R. H. R.: Role of dietary energy supplementation in growth of children with chronic renal insufficiency. Brit. Med. J., *1*:416, 1977.
9. Bricker, N. S.: On the pathogenesis of the uremic state: an exposition of the "trade-off hypothesis." New Engl. J. Med., *286*:1039, 1972.
10. Broyer, M., Kleinknecht, G., Loirat, C., et al.: Growth in children treated with long-term hemodialysis. J. Pediatr., *84*:642–649, 1974.
11. Burns, J., Cresswell, E., Ell, S., et al.: Comparison of the effects of keto acid analogues and essential amino acids on nitrogen homeostasis in uremic patients on moderately protein-restricted diets. Amer. J. Clin. Nutr. *31*:1767–75, 1978.
12. Canham, J. E., Numes, W. T., and Eberlin, E. W.: Electroencephalographic and central nervous system manifestations of B_6 deficiency and induced B_6 dependency in normal human adults. Proc. VI Intl Congr Nutr, E. and S. Livingstone, Edinborough, 1964, p. 537.
13. Chanarin, I.: The Megaloblastic Anemias. Oxford, Blackwell, 1959.
14. Chang, I. H., Harrill, I., and Gifford, E. D.: Influence of zinc and vitamin D on bone constituents of the rat. Metabolism, *18*:625, 1969.
15. Chantler, C., Counahan, R., El-Bishte, M. M., et al.: Growth in renal failure. Brit. Med. J., *1*:773–776, 1977.
16. Chantler, C., and Holliday, M. A.: Growth in children with renal disease with particular reference to the effects of calorie malnutrition: A review. Clin. Nephrol., *1*:288, 1973.
17. Coleman, A. J., et al.: Mechanism of salt wastage in chronic renal disease. J. Clin. Invest., 45:1116, 1966.
18. Coles, G. A.: Body composition in uremia. Quart. J. Med., *41*:25–47, 1971.
19. Committee on Nutrition, American Academy of Pediatrics: Salt intake and eating patterns of infants and children in relation to blood pressure. Pediatrics, 53:115, 1974.
20. Condon, C. J., and Freeman, R. M.: Zinc metabolism in renal failure. Ann. Intern. Med., 73:531, 1970.
21. Cotton, J. R., Woodward, T., Carter, N. W., et al.: Resting skeletal muscle membrane potential as an index of uremic toxicity. J. Clin. Invest., *63*:501–506, 1979.
22. Coursin, D. B.: Convulsive seizures in infants with pyridoxine-deficient diet. J.A.M.A., *154*:406, 1954.
23. Danovich, G. M., Bourgoinie, J., and Bricker, N. S.: Reversibility of the "salt-losing" tendency of chronic renal failure. New Engl. J. Med., *296*:14, 1977.
24. Dobbelstein, H., Korner, W. F., Mempel, W., et al.: Vitamin B_6 deficiency in uremia and its implications for the depression of immune response. Kidney Intl., 5:233, 1974.
25. El Bishte, M. M., Counahan, R., Stimmler, L., et al.: Abnormalities in plasma lipids in children on regular hemodialysis. Arch. Dis. Child., 52:932–936, 1977.
26. Elsborg, L.: The intestinal absorption of folic acid. Arhus, 1973.
27. FAO/WHO Expert Committee Report: Energy and Protein requirements. WHO Tech Report Series no. 522. Geneva, World Health Organization, 1973.
28. Federal Register, 36:684206845 (April 19), 1971.
29. Ford, J., Phillips, M. E., Joye, F. E., et al.: Nitrogen balance in patients with chronic renal failure on diets containing varying quantities of protein. Brit. Med. J., *1*:735–740, 1969.
30. Fürst, P., Ahlberg, M., Alvestrand, A., et al.: Principles of essential amino acid therapy in uremia. Amer. J. Clin. Nutr., *31*:1744–1755, 1978.

31. Giovannetti, S., and Maggiore, Q.: A low nitrogen diet with proteins of high biological value for severe chronic uremia. Lancet, *1*:1000, 1964.
32. Grupe, W. E., Kopito, L. E., Lazurus, J. M., et al.: Copper and zinc depletion in end stage renal disease (ESRD). (Abstr.) Pediat. Res., *10*:439, 1976.
33. Hampers, C. L., Streiff, R., Nathan, D. G., et al.: Megaloblastic hematopoiesis in uremia and in patients on long-term hemodialysis. New Engl. J. Med., *276*:551, 1967.
34. Haussler, M. R., and McCain, T. A.: Basic and clinical concepts related to vitamin D metabolism and action. New Engl. J. Med., *297*:974, 1979.
35. Hawkins, W. W., and Barsky, J.: An experiment on human vitamin B_6 deprivation. Science, *108*:284, 1948.
36. Hemmeloff Anderson, K. E.: Folic acid status of patient with chronic renal failure maintained by dialysis. Clin. Nephr., *8*:510, 1977.
37. Herbert, V.: The vitamins: Folic acid and vitamin B_{12}. *In* Goodhart, R. S., and Shils, M. E., eds.: Modern Nutrition in Health and Disease. Lea and Febiger, Philadelphia, 1973.
38. Holliday, M. A.: Calorie deficiency in children with uremia: Effect upon growth. Pediatrics, *50*:590–597, 1972.
39. Holliday, M. A.: Growth retardation in children with renal disease. *In* Edelmann, C. M., Jr., ed. Pediatric Kidney Disease. Little, Brown and Company, Boston, 1978, Vol. I. pp. 331–334.
40. Holliday, M. A.: Management of the child with renal insufficiency. *In* Lieberman, E., ed.: Clinical Pediatric Nephrology. Philadelphia, J. B. Lippincott Co., 1976.
41. Holliday, M. A., Wassner, S., and Ramirez, J.: Intravenous nutrition in uremic children with protein-energy malnutrition. Amer. J. Clin. Nutr., *31*:1854–1860, 1978.
42. Hyne, B. E. B., Fowell, E., and Lee, H. A.: The effect of caloric intake on nitrogen balance in chronic renal failure. Clin. Sci., *43*:679–688, 1972.
43. Ibels, L. S., Simmons, L. A., King, J. O., et al.: Studies on the nature and causes of hyperlipidemia in uremia, maintenance dialysis and renal transplantation. Quart. J. Med., *44*:601–614, 1975.
44. Jennette, J. C., and Goldman, I. D. Inhibition of membrane transport of folates by anions retained in uremia. J. Lab. Clin. Med., *86*:834, 1975.
45. Kaplan, M. A., et al.: Reversal of hyperparathyroidism in response to dietary phosphorus restriction in the uremic dog. Kidney Intl., *15*:43, 1979.
46. Keys, A., et al.: The Biology of Human Starvation. Minneapolis, Univ. Minnesota Press, 1950.
47. Kleeman, C. R., and Better, O. R.: Disordered divalent ion metabolism in kidney disease: Comments on pathogenesis and treatment. Kidney Intl., *4*:73, 1973.
48. Kluthe, R., Lüttgen, F. M., Capetianu, T., et al.: Protein requirements in maintenance hemodialysis. Amer. J. Clin. Nutr., *31*:1812, 1978.
49. Kopple, J. D.: Abnormal amino acid and protein metabolism in uremia. Kidney Intl., *14*:340–348, 1978.
50. Kopple, J. D., and Coburn, J. W.: Metabolic studies of low protein diets in uremia. I. Nitrogen and potassium. Medicine, *52*:583–595, 1973.
51. Kopple, J. D., Mercurio, K. C., and Card, B. K.: 6th Intl. Cong. Nephrol., Florence. Abstr. No. 906, 1975.
52. Lasker, N., Harvey, A., and Baker, H.: Vitamin levels in hemodialysis and intermittent peritoneal dialysis. Trans. Am. Soc. Artif. Intern. Organs, *9*:51, 1963.
53. Letteri, J. M., Ellis, K. J., Asad, S. N., et al.: Serial measurement of total body potassium in chronic renal disease. Amer. J. Clin. Nutr., *31*:1937–1944, 1978.
54. MacKenzie, J. C., Ford, J. E., Waters, A. H., et al.: Erythropoiesis in patients undergoing regular dialysis treatment (R.D.T.) without transfusion. Proc. Eur. Dial. Transplant Assoc. (Dublin), *5*:172, 1968.
55. Mahler, D. J., Walsh, J. F., and Haynie, G. D.: Magnesium, zinc, and copper in dialysis patients. Amer. J. Clin. Path., *56*:17, 1971.
56. Mansouri, K., Halsted, J. A., and Gombos, E. A.: Zinc, copper, magnesium and calcium in dialyzed and nondialyzed uremic patients. Arch. Intern. Med., *125*:88, 1970.
57. Moore, C. V.: Iron. *In* Goodhart, R. S. and Shils, M. E. eds.: Modern Nutrition in Health and Disease. Philadelphia, Lea and Febiger, 1973, p. 299.
58. National Research Council, Food and Nutrition Board: Recommended Dietary Allowances. 8th ed., publication no. 2216. National Academy of Science, Washington, D.C., 1974.
59. Potter, D. E., Broyer, M., Chantler, C., et al.: Measurement of growth in children with renal insufficiency. Kidney Intl., *14*:378–382, 1978.
60. Raskin, N. H., and Fishman, R. A. Pyridoxine-deficiency neuropathy due to hydralazine. New Engl. J. Med., *273*:1182, 1965.
61. Roche, A. F.: Growth assessment in abnormal children. Kidney Intl., *14*:369–377, 1978.

62. Rudolph, H., Alfrey, A. C., and Smythe, W. R.: Muscle and serum trace element profile in uremia. Trans. Am. Soc. Artif. Intern. Organs, *19*:456, 1973.
63. Sanfelippo, M. L., Swenson, R. S., and Reaven, G. M.: Reduction of plasma triglycerides by diet in subjects with chronic renal failure. Kidney Intl., *11*:54–61, 1977.
64. Schreiner, G. E., and Maher, J. F.: Uremia: Biochemistry, Pathogenesis and Treatment. Charles C Thomas, 1961, Springfield.
65. Siddiqui, J., Freeburger, R., and Freeman, R. M.: Folic acid, hypersegmented polymorphonuclear leukocytes and the uremic syndrome. Amer. J. Clin. Nutr., *23*:11, 1970.
66. Silva, P., Brown, R. S., and Epstein, F. H.: Adaptation to potassium. Kidney Intl., *11*:466–475, 1977.
67. Simmons, J. M., Wilson, C. J., Potter, D. E., et al.: Relation of caloric deficiency to growth failure in children on hemodialysis and the growth response to caloric supplementation. New Engl. J. Med., *285*:653–656, 1971.
68. Skoutakis, V. A., Acchiardo, S. R., Meyer, M. D., et al.: Folic acid dosage for chronic hemodialysis patients. Clin. Pharm. Therapeut., *18*:200, 1975.
69. Slatapolsky, E., et al.: Content of phosphate excretion in uremic man. J. Clin. Invest., *47*:1865, 1968.
70. Slatopolski, E., et al.: On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using proportional reduction of dietary phosphorus intake. Kidney Intl., *2*:1947, 1972.
71. Slatopolsky, E., Elkan, I. O., Weerts, C., et al.: Studies on the characteristics of the control system governing sodium excretion in uremic man. J. Clin. Invest., *47*:521, 1968.
72. Spady, D. W., Payne, P. R., Picou, D., et al.: Energy balance during recovery from malnutrition. Amer. J. Clin. Nutr., *29*:1076, 1976.
73. Spannuth, C. L., Warnock, L. G., Wagner, C., et al.: Increased metabolic clearance of pyridoxal 5-phosphate in uremia. Clin. Res., *24*:412A, 1976.
74. Stickler, G. B., and Bergen, B. J.: A review; short stature in renal disease. Pediatr. Res., *7*:978, 1973.
75. Stone, W. J., Warnock, L. G., and Wagner, C.: Vitamin B_6 deficiency in uremia. Amer. J. Clin. Nutr., *28*:950, 1975.
76. Sullivan, J. F., and Eisenstein, A. B.: Ascorbic acid depletion in patients undergoing chronic hemodialysis. Amer. J. Clin. Nutr., *23*:1339, 1970.
77. Swenseid, M. E.: Nutritional implications of renal disease. III. Nutritional needs of patients with renal disease. J. Amer. Diet. Assoc., *70*:488, 1977.
78. Talbot, N. B., Crawford, J. D., Kerrigan, G. A., et al.: Application of homeostatic principles to the practice of parenteral fluid therapy. New Engl. J. Med., *252*:856, 898, 1955.
79. Tamura, T., Shane, B., Baer, M. T., et al.: Absorption of mono- and polyglutamyl folates in zinc depleted man. Amer. J. Clin. Nutr., *31*:1984, 1978.
80. Van Ypersele de Strihov, C.: Potassium homeostasis in renal failure. Kidney Intl., *11*:491–504, 1977.
81. Walser, M.: Keto acid therapy in chronic renal failure. Nephron, *21*:56–74, 1978.
82. Weber, H. P., Romalin, A., Michalk, D., et al.: Gesant Korperkaliumunlersuchungen bei Kinder mit chronischer Niereninsuffizienz. Monatsschr. Kinderheilkd., *125*:329–330, 1977.
83. West, C. D., and Smith, W. C.: An attempt to elucidate the cause of growth retardation in renal disease. Amer. J. Dis. Child., *91*:460, 1956.
84. Whitehead, V. M., Comty, C. H., Posen, G. A., et al.: Homeostasis of folic acid in patients undergoing maintenance hemodialysis. New Engl. J. Med., *279*:970, 1968.

University of California
Children's Renal Center
400 Parnassus Avenue
San Francisco, California 94143

Nutrition in the Alcoholic

*Mark A. Korsten, M.D.,**
*and Charles S. Lieber, M.D.***

The recognition and correction of nutritional depletion is a major objective in the management of alcoholism. Indeed, in most developed areas of the world, alcoholism remains one of the few causes of florid nutritional deficiency states. Alcohol† and nutrition may interact at various levels. First, by displacing food from the diet and suppressing appetite, alcohol often decreases the ingestion of essential nutrients. Second, by injuring the liver, pancreas or bowel, alcohol may compromise the digestive and absorptive functions of the gastrointestinal tract. Third, by its obligatory breakdown to acetaldehyde in the liver, alcohol alters the metabolism and activation of other dietary constituents.

Given the close association of alcoholism with malnutrition, it was at one time assumed (erroneously) that nutrient deficiency was solely responsible for the medical sequelae of alcohol abuse. The fatty liver complicating protein and lipotrope deficiency (in rats)[14] and kwashiorkor (in humans) appeared to support this notion. However, more recently it has been demonstrated both in animals and in human volunteers that alcohol has direct toxicity and can have a variety of injurious effects. Of these, the hepatic toxicity of alcohol has been most convincingly established.[23, 33-35, 38, 58-60] In human beings chronic administration of alcohol results in hepatic steatosis despite nutritionally adequate diets and lipotrope (choline) supplementation. Similar conclusions were derived from the long term feeding of alcohol to baboons. The entire spectrum of alcohol-related hepatic injury (steatosis and cirrhosis) was reproduced in this species in the absence of malnutrition.[38] This evidence for the direct toxicity of ethanol has an important clinical consequence. The physician must warn his patient that

*Assistant Professor of Medicine, Mount Sinai School of Medicine; Staff Physician, Veterans Administration Hospital, Bronx, New York.
**Professor of Medicine and Pathology, Mount Sinai School of Medicine; Chief, Section of Liver Disease and Nutrition, and Director, Alcoholism Research and Treatment Center, Veterans Administration Hospital, Bronx, New York

†Ethanol and alcohol are used interchangeably in this article.

adequate or even enriched nutrition will not preclude serious medical complications of alcoholism.

Alcohol as a Nutrient

The complete combustion of 1 gram of alcohol yields 7.1 calories. In vivo, however, ethanol and other dietary constituents do not behave as caloric equivalents, since isocaloric substitution of ethanol for dietary carbohydrate results in a decline in body weight.[52] To interpret this observation, a brief review of the pathways of alcohol metabolism is helpful (Fig. 1). At low levels of alcohol, oxidation of alcohol to acetaldehyde is mediated primarily by alcohol dehydrogenase, a cytosolic enzyme found in hepatic parenchymal cells. In this reaction, the cofactor NAD is reduced to NADH. Subsequent oxidation of NADH is coupled to ATP generation within the mitochondrial electron transport chain. At higher levels of alcohol, another pathway of alcohol oxidation may become quantitatively significant. This pathway has been identified within the microsomal fraction of the hepatocyte and has cofactor requirements different from that of alcohol dehydrogenase.[31, 32] This microsomal ethanol oxidizing system (MEOS) does not result in the production of NADH and is not coupled to oxidative phosphorylation. By its failure to conserve chemical energy, ethanol metabolized by MEOS constitutes "empty" calories. To the extent that MEOS participates in ethanol metabolism, it may contribute to the weight loss observed in human beings upon isocaloric substitution of carbohydrate by ethanol.[52]

Effects of Alcohol on the Absorption and Digestion of Nutrients

STOMACH. Alcohol affects many facets of gastric physiology including acid secretion,[6] mucosal permeability,[8] and gastric emptying.[4] The pathogenesis of acute gastritis probably depends on one or more of these factors. Davenport has shown that by disruption of the gastric "mucosal barrier," alcohol permits rapid diffusion of hydrogen ions into the gastric mucosa and liberation of histamine.[9] Acute gastritis is a common clinical complication of alcoholism, patients noting anorexia, abdominal pain, and at times hematemesis. In addition, acute gastritis may exacerbate malnutrition by suppressing appetite. By increas-

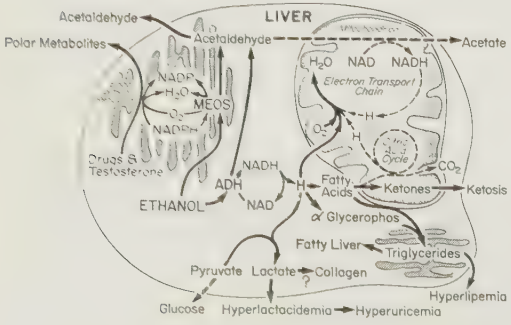


Figure 1.

ing gastric acid secretion, alcohol may also enhance the absorption of ferric ion (but not ferrous or hemoglobin iron).[5] If absorption is excessive, deposition of iron in tissues may be injurious and aggravate the effects of alcohol.

PANCREAS. Many theories have been offered to explain the occurrence of pancreatic insufficiency in the alcoholic. The older hypotheses proposed that stimulation of pancreatic flow against increased resistance resulted in hypertension, ductular rupture, and glandular autodigestion.[10, 51] According to this theory, pancreatic stimulation depends on acid-mediated release of the hormone secretin, and increased ductal resistance is due to alcohol-induced duodenitis or increased tone in the sphincter of Oddi. More recently, it has been suggested that chronic alcohol consumption may alter the composition of pancreatic juice by increasing cholinergic tone[66] and increasing the release of cholecystokinin.[47] Hypersecretion of protein in the juice would result from these factors. Subsequent precipitation of proteinaceous plugs and their calcification might, in turn, lead to ductular blockage, metaplasia, and rupture. Whether chronic pancreatitis in the alcoholic is due to alcohol per se or concomitant malnutrition remains an important but ill-defined aspect of this disorder. Although protein plugs are common in the chronic pancreatitis of kwashiorkor (implying that poor nutrition might also be an etiologic factor in alcoholic pancreatitis), epidemiologic surveys of premorbid dietary patterns in alcoholic chronic pancreatitis have revealed that these patients had diets that were enriched, rather than deficient in protein and fat.[61]

Chronic pancreatitis has important effects on nutrition. When pancreatic damage is sufficiently extensive, hyposecretion of bicarbonate and enzymes may result in maldigestion of fat and protein. Despite steatorrhea, deficiencies of fat-soluble vitamins are unusual in patients with pancreatic insufficiency.[11] Defects in the absorption of vitamin B_{12} have also been described in chronic pancreatitis.[68] Vitamin B_{12} malabsorption has been attributed to a failure of pancreatic juice to inactivate non-intrinsic factor binders of the vitamin.[41] As expected, pancreatic extract is effective in restoring vitamin B_{12} absorption. Since vitamin B_{12} deficiency is unusual in patients with chronic pancreatitis, the clinical relevance of these findings is uncertain.

LIVER. As mentioned above, attention was focused early on malnutrition as an etiologic factor in alcoholic liver injury given the poor food intake of many alcoholics. However, it is now established that malnutrition does not play the primary role in the pathogenesis of alcoholic liver disease. Indeed, the importance of alcohol consumption per se has been repeatedly confirmed in epidemiologic,[24, 48, 49] animal, and human studies. Recently, chronic ingestion of daily amounts as low as 40 gm of alcohol in men and 20 gm in women were found to be associated with a statistically significant increase in the incidence of cirrhosis, even in well nourished populations.[48, 49] Malnutrition, however, under certain conditions, may potentiate the hepatotoxic effects of alcohol.[21, 36]

Apart from its profound effects on intermediary metabolism, alco-

holic liver injury may disrupt digestive processes by altering bile salt metabolism. Changes related to alcoholic cirrhosis include a decrease in cholic acid synthesis and a decrease in total bile acid pool size.[72, 73] If the level of bile salts in the bowel lumen falls below the critical concentration needed for micelle formation, cirrhosis may result in steatorrhea. Although steatorrhea is common in the cirrhotic patient, the incidence may be inflated by coexistent (and subclinical) pancreatic disease and therapeutic measures such as neomycin.

SMALL BOWEL. Small bowel function and morphology are altered by a direct effect of alcohol and concomitant nutrient deficiencies. These two factors may interact synergistically to further impair nutrient absorption (Figure 2). Impaired uptake of fat, D-xylose, folic acid, vitamin B_{12} and thiamine has been shown in alcoholics.[13, 40, 43, 57, 65, 67] After periods of abstinence and nutritional repletion, improved absorption of these substances has been reported. However, such data do not permit an assessment of the relative importance of alcohol and associated malnutrition in the pathogenesis of the malabsorption. The absorption of vitamin B_{12} and folic acid has been studied in this context. In well-nourished human volunteers, the chronic administration of ethanol had no significant effect on the absorption of folic acid. Under similar conditions of alcohol administration, decreased uptake of vitamin B_{12} was detected and persisted despite supplementary intrinsic factor and pancreatic extract. An extensive review of this subject has been published.[3]

Effect of Alcohol on the Activation of Nutrients

As mentioned before, most ethanol is metabolized to acetaldehyde in the liver. Among the known toxic effects of acetaldehyde, interference with pyridoxine activation may have an important nutritional consequence. Acetaldehyde may alter pyridoxine metabolism by displacing pyridoxal phosphate (the active coenzyme form of pyridoxine) from its cytosolic binding protein.[70] Such displacement may favor the hydrolysis of pyridoxal phosphate by pyridoxal phosphatase and result in a net decrease in the activation of the vitamin. Vitamin D metabolism also depends on hepatic activation and may be disturbed in the alcoholic patient. For example, 25-hydroxylation of cholecalciferol may be reduced in alcoholic liver injury[2] (although this was not confirmed in a recent study)[53] and degradation of activated vitamin D may be enhanced by alcohol-induced mixed-function oxidases. Thus, abnormal activation may be superimposed on inadequate dietary intake and defective intestinal absorption of vitamin D and contribute to the increased incidence of fractures[46] and osteonecrosis[63] observed in alcoholic populations.

Carbohydrate, Lipid, and Protein Metabolism in the Alcoholic

The alcoholic often suffers from protein-calorie malnutrition because of inadequate ingestion. Pure deficiencies of either protein or carbohydrate are, of course, unusual. Diets deficient in these nutrients may result in muscle-wasting and edema. Protein (albumin) synthesis

by the liver is reduced[57] and results in low serum protein levels. Protein deficiency may also lead to steatosis in children and this is one of the manifestations of kwashiorkor. However, in adolescent baboons, protein restriction to 7 per cent of total calories did not result in liver injury even after 19 months.[37] Moreover, protein supplementation did not prevent ethanol from producing fat accumulation in human volunteers.[25] Thus, even in the absence of protein deficiency, ethanol is capable of producing hepatic steatosis in man. Experimentally, alcohol may be nitrogen-sparing when given as supplementary calories but decreases positive nitrogen balance when given as an isocaloric substitute for carbohydrate.[20, 55] Ethanol may also block protein synthesis, and alter the transport, uptake, and clearance of amino acids.

Carbohydrate homeostasis is impaired in alcoholics with or without associated liver injury. Autonomic dysfunction, impaired gluconeogenesis (especially from alanine), glycogen depletion, and other endocrine effects have been attributed to ethanol.[1] Alcoholism apparently has no effect on the absorption and digestion of carbohydrates.[12] Lipid metabolism in the alcoholic is affected to the extent that ethanol oxidation results in an increased NADH/NAD ratio. An increase in this index of the cytosolic redox state secondarily retards fatty acid oxidation (Fig. 2) and favors the formation of triglycerides.[26] When incorporated into lipoproteins, triglycerides may appear as very low density lipoproteins in the serum. Some patients, especially those with familial Type IV hyperlipidemia, may exhibit a marked sensitivity to the lipemic effects of alcohol. Indeed, ethanol may unmask a subclinical hyperlipidemia and should be excluded as an etiologic factor in patients with lipid disorders.

Alcohol-Related Deficiency Syndromes

NEUROLOGIC COMPLICATIONS. The alcoholic may suffer from a variety of neurologic problems including peripheral polyneuropathy, the Wernicke-Korsakoff syndrome, nutritional amblyopia and cerebel-

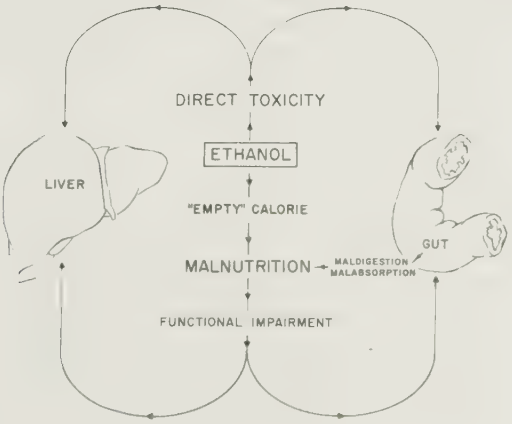


Figure 2.

lar degeneration. Although nutritional depletion (especially of B vitamins) appears to be important in the pathogenesis of these disorders, ethanol, or its breakdown product acetaldehyde, has been shown to have direct toxic effects on the nervous system.[69]

Alcoholic polyneuropathy presents with weakness and paresthesias (in a glove and stocking distribution) of the distal lower extremities. Vibration sense in the toes and deep tendon reflexes in the ankles are often diminished. The Wernicke-Korsakoff syndrome is characterized by ophthalmoplegia (horizontal nystagmus and paresis of lateral gaze), ataxia, and disturbed mentation. Confabulation commonly accompanies deficits in memory and cognitive function. Thiamine administration (25 to 50 mg) usually results in dramatic resolution of signs and symptoms. Nutritional amblyopia is a condition that may complicate all forms of chronic malnutrition. Blurred vision, photophobia and retrobulbar pain are usually noted. Signs include central or paracentral scotomata. The pathogenesis of this disorder has not been attributed to a specific B vitamin deficit. Abstinence, nutritional support, and multivitamin B supplementation generally improves visual acuity. Cerebellar degeneration is manifested as an unsteady and lurching gait. Ataxia of the lower extremities is apparent on physical examination. At least in part, the ataxia may resolve with abstinence, better nutrition, and B vitamin repletion.

HEMATOLOGIC COMPLICATIONS. The serum level of folic acid is commonly depressed in chronic, malnourished alcoholics.[75] Folate deficiency causes leukopenia and thrombocytopenia as well as megaloblastic anemia. Intestinal megaloblastosis may accompany marrow megaloblastosis and further impair the uptake of folic acid.[15] In addition to these factors, alcohol itself has a suppressive effect on the bone marrow by interfering with folate metabolism.[64]

Sideroblastic changes (iron deposition in mitochondria) in red cell precursors are also relatively common in the folate deficient chronic alcoholic.[17] Macrocytic or hypochromic microcytic anemias are found on the peripheral smear in patients with sideroblastic marrows. Large doses of pyridoxine may be efficacious in this condition.[18] As little as 1 mg of pyridoxine per day prevents sideroblastic changes during administration of ethanol to well-nourished volunteers.[39]

Coagulation may be abnormal in the alcoholic patient. Several causes may be identified. The synthesis of clotting factors may be subnormal due to liver injury and this may be exacerbated by vitamin K deficiency (arising from dietary lack, malabsorption or altered intestinal flora). Other causes of coagulopathy include hypersplenism, intravascular consumption of clotting factors, and a direct effect of alcohol on platelet production and function.

CARDIOVASCULAR COMPLICATIONS. Alcoholic cardiomyopathy appears to result from a direct action of ethanol and is not prevented by good nutrition.[16] However, dietary deficiency may predispose to cobalt cardiomyopathy in heavy beer drinkers.[19] Before this toxicity was suspected, cobalt chloride was added to beer to stabilize its foam.

Alcoholic cardiomyopathy presents with signs and symptoms of

congestive heart failure. In addition to the usual treatment modalities (salt restriction, diuretics, digitalis), abstinence and prolonged bed rest are effective therapies.[42]

Thiamine deficiency predisposes to beriberi heart disease but, at present, is rare even in malnourished chronic alcoholics. The cardiac manifestations of beriberi and alcoholic cardiomyopathy are similar. However, associated symptoms of thiamine deficiency (e.g., neuropathy and psychosis) permit a differentiation. Administration of thiamine rapidly reverses the signs and symptoms of beriberi.

ONCOLOGIC COMPLICATIONS. Epidemiologic studies support an association of alcoholism with cancers of the head and neck, esophagus, liver, and colon. The respective roles of alcohol and associated nutritional deficiency in carcinogenesis is an area of current investigation. Since it has been established that microsomal systems activate a variety of procarcinogens,[44] the induction of microsomal enzyme activity by ethanol,[29, 30] with an associated increased conversion of procarcinogens to carcinogens and enhanced mutagenicity,[62] may constitute a level at which alcohol and carcinogens interact. It is also possible that carcinogenesis may be influenced by the nutritional consequences of alcoholism since it is well-known that diet modifies tumor formation in laboratory animals.[7, 74, 76, 77] In human beings, chronic deficiency of iron may play a role in the etiology of gastric cancer,[71] and zinc deficiency has been related to the high incidence of esophageal carcinoma in Iran.[22]

Nutritional Support of the Alcoholic

The basic goal of nutritional therapy in the alcoholic patient is to prevent or correct nutritional deficiencies, especially of vitamins. Concerning proteins and fats, however, the situation is less clearcut. High protein diets do not appear indicated and may exacerbate symptoms of hepatic encephalopathy in the alcoholic with cirrhosis. Protein intake should not exceed the protein tolerance of the cirrhotic patient or the recommended daily amount,[45] whichever is lower. Similarly, choline supplementation cannot be recommended since it was not found efficacious under controlled experimental conditions. Finally, since in patients with pancreatic insufficiency, fat may intensify symptoms of steatorrhea, dietary fat must be employed as judiciously as the use of protein.

SUMMARY

Effective management of nutritional problems in the alcoholic patient requires that the clinician understand the complex interaction of alcohol and nutrition. Nutritional deficiencies should be prevented and, if present, corrected. However, experimental, clinical, and epidemiological evidence indicates that despite adequate diets, ethanol has direct toxic effects on the digestion, absorption and activation of foodstuff. Furthermore, recent studies have shown that even in well-

nourished populations relatively small amounts of alcohol may have cirrhogenic potential. For these reasons, the overall approach to the management of the alcoholic must involve the control of alcohol intake as well as the prevention and correction of nutritional disturbances.

REFERENCES

1. Arky, R. A.: The effect of alcohol on carbohydrate metabolism: carbohydrate metabolism in alcoholics. *In* Kissin, B., and Begleiter, H., eds.: The Biology of Alcoholism. New York, Plenum Press. Vol. I, 1974, p. 197.
2. Avioli, L. V., and Haddad, J. G.: Vitamin D: current concepts. Metabolism, 22:507, 1973.
3. Baraona, E., and Lindenbaum, J.: Metabolic effects of alcohol on the intestine. *In* Lieber, C. S., ed.: Metabolic Aspects of Alcoholism. Baltimore, University Park Press, 1977, p. 81.
4. Barboriak, J. J., and Meade, R. C.: Effect of alcohol on gastric emptying in man. Amer. J. Clin. Nutr., 23:1151, 1970.
5. Charlton, R. W., Jacobs, P., Seftel, H., et al.: Effect of alcohol on iron absorption. Brit. Med. J., 2:1427, 1964.
6. Chey, W. Y., Kosay, S., and Lorber, S. H.: Effects of chronic administration of ethanol on gastric secretion of acids in dogs. Amer. J. Dig. Dis., *17*:153, 1972.
7. Chu, E. W., and Malmgren, R. A.: Inhibitory effect of vitamin A on the induction of tumors of forestomach and cervix in the Syrian hamster by carcinogenic polycyclic hydrocarbons. Cancer Res., 25:884, 1965.
8. Davenport, H. W.: Ethanol damage to canine oxyntic glandular mucosa. Proc. Soc. Exper. Biol. Med., *126*:657, 1967.
9. Dragstedt, C. S., Gray, J. S., Lawton, A. H., et al.: Does alcohol stimulate gastric secretion by liberating histamine? Proc. Soc. Exper. Biol. Med., *43*:26, 1940.
10. Dreiling, D. A., Richman, A., and Fradkin, N. F.: The role of alcohol in the etiology of pancreatitis: A study of the effect of intravenous ethyl alcohol on the external secretion of the pancreas. Gastroenterology, *20*:636, 1952.
11. Evans, W. B., and Wollaeger, E. E.: Incidence and severity of nutritional deficiency states in chronic exocrine pancreatic insufficiency: comparison with non-tropical sprue. Amer. J. Dig. Dis., *11*:594, 1966.
12. Gabuzda, G. J.: Nutrition and liver disease. MED. CLIN. N. AMER., 54:1455, 1970.
13. Halsted, C. H., Robles, E. A., and Mezey, E.: Decreased jejunal uptake of labeled folic acid (^{3}H-PGA) in alcoholic patients: role of alcohol and nutrition. New Engl. J. Med., 285:701, 1971.
14. Hartroft, S. W., and Porta, E. A.: Alcohol, diet and experimental hepatic injury. Can. J. Physiol. Pharmacol., *46*:463, 1968.
15. Hermos, J. A., Adams, W. H., Liu, Y. K., et al.: Mucosa of the small intestine in folate-deficient alcoholics. Ann. Intern. Med., 76:957, 1972.
16. Hillman, R. W.: Alcoholism and malnutrition. *In* Kissin, B., and Begleiter, H., eds.: The Biology of Alcoholism. New York, Plenum Press, Vol. 3, 1974, p. 549.
17. Hines, J. D.: Reversible megaloblastic and sideroblastic marrow abnormalities in alcholic patients. Brit. J. Haematol., *16*:87, 1969.
18. Hines, J. D., and Cowan, D. H.: Studies on the pathogenesis of alcohol-induced sideroblastic bone-marrow abnormalities. New Engl. J. Med., 283:441, 1970.
19. Kesleot, H., Roelandt, J., Willems, S., et al.: An inquiry into the role of cobalt in the heart disease of chronic beer drinkers. Circulation, 37:854, 1968.
20. Klatskin, G.: The effect of ethyl alcohol on nitrogen excretion in the rat. (Abstract.) Yale J. Biol. Med., 34:124, 1961.
21. Klatskin, G., Krehl, W. A. and Conn, H. O.: The effect of alcohol on the choline requirement. I. Changes in the rat's liver following prolonged ingestion of alcohol. J. Exper. Med., *100*:605, 1954.
22. Kmet, J., and Mahboubi, E.: Esophageal cancer in the Caspian littoral of Iran: Initial studies. Science, *175*:846, 1972.
23. Lane, B. P., and Liever, C. S.: Ultrastructural alterations in human hepatocytes following ingestion of ethanol with adequate diets. Amer. J. Pathol., *49*:593, 1966.
24. Lelbach, W. K.: Leberschaden bei chronischem Alkoholismus. Acta Hepatosplenol. (Stuttg), *14*:9, 1967.

25. Liever, C. S.: Chronic alcoholic hepatic injury in experimental animals and man: biochemical pathways and nutritional factors. Fed. Proc., 26:1443, 1967.
26. Lieber, C. S.: Effects of ethanol upon lipid metabolism. Lipids, 9:103, 1974.
27. Lieber, C. S.: Alcohol and malnutrition in the pathogenesis of liver disease. J.A.M.A., 233:1077, 1975.
28. Lieber, C. S.: Pathogenesis and early diagnosis of alcoholic liver injury. New Engl. J. Med., 298:888, 1978.
29. Lieber, C. S., and DeCarli, L. M.: Ethanol oxidation by hepatic microsomes; adaptive increase after ethanol feeding. Science, 162:917, 1968.
30. Lieber, C. S., and DeCarli, L. M.: Effect of drug administration on the activity of the hepatic microsomal ethanol oxidizing system. Life Sci., 9:267, 1970.
31. Lieber, C. S., and DeCarli, L. M.: Hepatic microsomal ethanol-oxidizing system: In vitro characteristics and adaptive properties in vivo. J. Biol. Chem., 245:2505, 1970.
32. Lieber, C. S., and DeCarli, L. M.: The role of the hepatic microsomal ethanol oxidizing system (MEOS) for ethanol metabolism in vivo. J. Pharmacol. Exper. Ther., 181:279, 1972.
33. Lieber, C. S., and DeCarli, L. M.: An experimental model of alcohol feeding and liver injury in the baboon. J. Med. Primatology, 3:153, 1974.
34. Lieber, C. S., and Rubin, E.: Alcoholic fatty liver in man on a high protein and low fat diet. Amer. J. Med., 44:200, 1968.
35. Lieber, C. S., Jones, D. P., and DeCarli, L. M.: Effects of prolonged ethanol intake: production of fatty liver despite adequate diets. J. Clin. Invest., 44:1009, 1965.
36. Lieber, C. S., Spritz, N., and DeCarli, L. M.: Fatty liver produced by dietary deficiencies: its pathogenesis and potentiation by ethanol. J. Lipid Res., 10:283, 1969.
37. Lieber, C. S., DeCarli, L. M., Gang, H., et al.: Hepatic effect of long-term ethanol consumption in primates. *In* Goldsmith, E. I., and Moor-Jankowski, J., eds.: Medical Primatology. Basel, Karger, Part III, 1972, p. 270.
38. Lieber, C. S., DeCarli, L. M., and Rubin, E.: Sequential production of fatty liver, hepatitis and cirrhosis in sub-human primates fed ethanol with adequate diets. Proc. Natl. Acad. Sci., USA, 72:437, 1975.
39. Lindenbaum, J., and Lieber, C. S.: Hematologic effects of alcohol in man in absence of nutritional deficiency. New Engl. J. Med., 281:333, 1969.
40. Lindenbaum, J., and Lieber, C. S.: Effects of ethanol on the blood, bone marrow, and small intestine of man. *In* Roach, M. K., McIsaac, W. M., and Creaven, P. J., eds.: Biological Aspects of Alcohol. Austin, University of Texas Press, Vol. III, 1971, p. 27.
41. von der Lippe, G., Andersen, K.-J., and Schjonsby, H.: Pancreatic extract and the intestinal uptake of vitamin B_{12}. III. Stimulatory effect in the presence of a non-intrinsic factor vitamin B_{12} binder. Scand. J. Gastroenterol., 12:183, 1977.
42. McDonald, C. D., Burch, G. E., and Walsh, J. J.: Alcoholic cardiomyopathy managed with prolonged bed rest. Ann. Intern. Med., 74:681, 1971.
43. Mezey, E., Jow, E., Slavin, R. E., et al.: Pancreatic function and intestinal absorption in chronic alcoholism. Gastroenterology, 59:657, 1970.
44. Mitchell, J. R., and Jollow, D. J.: Role of metabolic activation in chemical carcinogenesis and in drug induced hepatic injury. *In* Gerok, W., and Sickinger, K., eds.: Drugs and the Liver. 3rd International Symposium, Schattauer Verlag, Stuttgart-New York, 1975, p. 395.
45. Munro, M. N.: Committee on dietary allowances. The National Research Council, National Academy of Sciences, Washington, D.C., 1978.
46. Nilsson, B. E.: Conditions contributing to fracture of the femoral neck. Acta Chir. Scand., 136:383, 1970.
47. Palasciano, G., Tiscornia, O., Hage, G., et al.: Chronic alcoholism and endogenous CCK-PZ. Biomedicine, 21:94, 1974.
48. Pequignot, G., Chabert, C., Eydoux, H., et al.: Augmentation du risque de cirrhose en fonction de la ration d'alcool. Revue de l'Alcoolisme, 20:191, 1974.
49. Pequignot, G., Tuyns, A. J., and Berta, J. L.: Ascitic cirrhosis in relation to alcohol consumption. Internat. J. Epidemiol., 7:113, 1978.
50. Phillips, G. B., and Davidson, C. S.: Nutritional aspects of cirrhosis in alcoholism — effect of a purified diet supplemented with choline. Ann. N.Y. Acad. Sci., 57:812, 1954.
51. Pirola, R. C., and Davis, A. E.: Effects of intravenous alcohol on motility of the duodenum and of the sphincter of Oddi. Aust. Ann. Med., 19:24, 1970.
52. Pirola, R. C., and Lieber, C. S.: The energy cost of the metabolism of drugs including alcohol. Pharmacology, 7:185, 1972.
53. Posner, D. B., Russell, R. B., Absood, S., et al.: Effective 25-hydroxylation of vitamin D_2 in alcoholic cirrhosis. Gastroenterology, 74:866, 1978.
54. Post, J., Benton, J. G., Breakstone, R., et al.: Effects of diet and choline on fatty infiltration of the human liver. Gastroenterology, 20:403, 1952.

55. Rodrigo, C., Antezana, C., and Baraona, E.: Fat and nitrogen balances in rats with alcohol-induced fatty liver. J. Nutr., *101*:1307, 1971.
56. Roggin, G. M., Iber, F. L., Kater, R. M. H., et al.: Malabsorption in the chronic alcoholic. Johns Hopkins Med. J., *125*:321, 1969.
57. Rothschild, M. A., Oratz, M., and Schreiber, S. S.: Albumin synthesis. New Engl. J. Med., *286*:749, 1972.
58. Rubin, E., and Lieber, C. S.: Experimental alcoholic hepatic injury in man: Ultrastructural changes. Fed. Proc., *26*:1458, 1967.
59. Rubin, E., and Lieber, C. S.: Alcohol-induced hepatic injury in non-alcoholic volunteers. New Engl. J. Med., *278*:869, 1968.
60. Rubin, E., and Lieber, C. S.: Fatty liver, alcoholic hepatitis and cirrhosis produced by alcohol in primates. New Engl. J. Med., *290*:128, 1974.
61. Sarles, H., Sarles, J.-C., Camatte, R., et al.: Observations of 205 confirmed cases of acute pancreatitis, recurring pancreatitis, and chronic pancreatitis. Gut, *6*:545, 1965.
62. Seitz, H. J., Garro, A. J., and Lieber, C. S.: Effect of chronic ethanol ingestion on intestinal metabolism and mutagenicity of benzo(α)pyrene. Biochem. Biophys. Res. Commun., *85*:1061, 1978.
63. Solomon, L.: Drug-induced arthropathy and necrosis of the femoral head. J. Bone Joint Surg. (Br.), *55*:246, 1973.
64. Sullivan, L. W., and Herbert, V.: Suppression of hematopoiesis by ethanol. J. Clin. Invest., *43*:2048, 1964.
65. Thomson, A. D., Baker, H., and Leevy, C. M.: Patterns of ^{35}S-thiamine hydrochloride absorption in the malnourished alcoholic patient. J. Lab. Clin. Med., *76*:34, 1970.
66. Tiscornia, O. M., Singer, M., Mendes de Oliveira, J. P., et al.: Exocrine pancreas response to a test meal in the dog. Amer. J. Dig. Dis., *22*:769, 1977.
67. Tomasulo, P. A., Kater, R. M. H., and Iber, F. L.: Impairment of thiamine absorption in alcoholism. Amer. J. Clin. Nutr., *21*:1340, 1968.
68. Toskes, P. P., Hansell, J., Cerda, J., et al.: Vitamin B_{12} malabsorption in chronic pancreatic insufficiency: Studies suggesting the presence of a pancreatic intrinsic factor. New Engl. J. Med., *284*:627, 1971.
69. Truitt, E. B., and Walsh, M. J.: The role of acetaldehyde in the actions of ethanol. *In* Kissin, B., and Begleiter, H., eds.: The Biology of Alcoholism. New York, Plenum Press, Vol. I, 1971, p. 161.
70. Veitch, R. L., Lumeng, L., and Li, T. K.: Vitamin B_6 metabolism in chronic alcohol abuse: The effect of ethanol oxidation on hepatic pyridoxal 5'-phosphate metabolism. J. Clin. Invest., *55*:1026, 1975.
71. Vitale, J. J., and Gottlieb, L. S.: Alcohol and alcohol-related deficiencies as carcinogens. Cancer Res., *35*:3336, 1975.
72. Vlahcevic, Z. R., Buhac, I., Farrar, J. T., et al.: Bile acid metabolism of cholic acid metabolism. I. Kinetic aspects of cholic acid metabolism. Gastroenterology, *60*:491, 1971.
73. Vlahcevic, Z. R., Juttijudata, P., Bell, C. C., et al.: Bile acid metabolism in patients with cirrhosis. II. Chronic and chenodeoxycholic acid metabolism. Gastroenterology, *62*:1174, 1972.
74. Weisburger, J. H.: Chemical carcinogenesis. *In* Casarett, L. S., and Doull, J., eds.: Toxicology, The Basic Science of Poisons. New York, Macmillan Press, 1975, p. 333.
75. Winawer, S. J., Sullivan, L. W., Herbert, V., et al.: The jejunal mucosa in patients with nutritional folate deficiency and megaloblastic anemia. New Engl. J. Med., *272*:892, 1965.
76. Wynder, E. L.: Nutrition and cancer. Fed. Proc., *35*:1309, 1976.
77. Wynder, E. L., and Chan, P. C.: The possible role of riboflavin deficiency in epithelial neoplasia. II. Effect on skin tumor development. Cancer, *26*:1221, 1970.

Veterans Administration Hospital
130 West Kingsbridge Road
Bronx, New York 10468

Hyperalimentation

*Josef E. Fischer, M.D.**

It is now more than 10 years since the initial successful application of total parental nutrition to patients using a central amino acids-glucose technique,[7, 8] and more than 25 years since successful nutritional support using a peripheral technique in which the principal source of calories was lipid.[37] Metabolic and nutritional support is among the most rapidly growing areas in clinical medicine, and these techniques have had a dramatic impact on patient care. Despite rapid progress, much remains to be done and the field remains, with some exception, one in which intuition is often used as a substitute for facts. In the following pages we will review briefly the state of the art of parenteral nutrition and attempt to delineate appropriate areas of future need and progress.

Route of Administration

The intravenous route of administration is unphysiological as compared with our normal mode of ingesting nutrients, the gut. One can make a good case teleologically and metabolically for nutrients being absorbed from the gut and being emptied into the portal vein, where they may be processed by the liver, which clears between 50 and 75 per cent of all glucose and amino acids presented to it, processing the nutritional material and preparing it for distribution at selected times to the periphery. This advantage is obviously lost when material is given into the superior vena cava. In addition, metabolic processes such as the transamination of amino acids may preferentially take place in the gut, an advantage which is also lost when material is given into the superior vena cava. The biological advantage of the gut is seen in those few isocaloric isonitrogenous studies in which identical amounts of food were given intravenously and orally; the gut had a decided advantage.[2] More recently, some investigators have begun to explore (once again) intraportal administration via the obliterated umbilical vein, claiming excellent results.[29] The complications of this

Christian R. Holmes Professor and Director, Department of Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio

Supported in part by Public Health Service Grants AM-15347 and AM-19124.

technique, however, and the potential disaster of portal vein thrombosis make it unlikely that this method will achieve wide acceptance.

Basic Principles in Parenteral Nutrition

The basic concept is the intravenous administration of sufficient quantities of calories and nitrogen, generally by continuous infusion. This takes place either by peripheral or central means. By peripheral one usually refers to the veins of the arm. Since dependence on glucose for the majority of caloric supply would render the solution sufficiently hypertonic so that sclerosis of peripheral veins results, a corollary of the peripheral technique is the utilization of large quantities of intravenous fat as the principal caloric source. The peripheral technique has limitations of calories and volume. In order to achieve 3000 calories for example, 1500 calories are given as 1500 cc of 10 per cent Intralipid. Another 4 liters of material containing 5 to 7 per cent dextrose and amino acids must be administered as well. In patients who are severely ill the peripheral technique probably has little application, as it is doubtful that fat is completely utilized under these circumstances. Secondly the caloric needs usually are greater than 3000 Kcal in patients with sepsis.

Most parenteral nutrition practice in the United States utilizes a central superior vena caval catheter, placed either in the internal jugular or the subclavian vein and terminating in the superior vena cava, just above the right atrium. The solutions usually contain 40 grams of amino acids per liter and hypertonic dextrose ranging between 23 and 47 per cent. Because the catheter tip is in the superior vena cava, the large volume of blood flow dilutes the hypertonic material probably as much as 1200 times even at maximal rates of intravenous infusion and prevents injury to the intima during administration. When fat is utilized by this technique it is generally to prevent essential fatty acid deficiency but not, in general, to supply calories.

Requirements for Nutrition

One of the advantages of parenteral nutrition is the ability to study such patients and derive accurate estimates of the requirements for nutrition. Parenteral nutrition has thus enabled us to study the requirements of such patients in a fairly detailed fashion.

NITROGEN It is generally accepted that 250 mg of nitrogen per kg per 24 hours is sufficient at least for maintenance of most patients. The actual figure is probably slightly below this, between 200 and 250 mg of nitrogen per kg. It is possible, indeed likely, in severe stress or sepsis that greater quantities of nitrogen are required, or that varying the qualitative aspects of amino acid solutions might be more valuable.[15]

CALORIE NITROGEN RATIO In order to achieve nitrogen balance and promote protein synthesis it is necessary to administer a non-protein caloric source in amounts sufficient to promote protein synthesis. This is generally referred to as a calorie : nitrogen ratio and is widely assumed to be somewhere between 150 and 180 non-protein calories per gram of nitrogen. Recent studies from this and other la-

boratories have confirmed that approximately 150 to 160 non-protein calories per gm of nitrogen are probably sufficient, at least under most circumstances, to promote optimal utilization of nitrogen.[28] It is not clear whether greater amounts of calories might be required in other situations such as acute tubular necrosis.[1]

FAT CALORIES VERSUS GLUCOSE CALORIES. One of the current controversies in parenteral nutrition, and one which is not entirely resolved, is the equivalence of carbohydrate and fat calories. Several recent investigations have suggested that whereas fat may not be utilized efficiently for calories in patients who are septic and severely stressed, it does appear, either for maintenance or in patients who are not severely stressed or septic, that fat, after a lag period of approximately 3 to 4 days, is equivalent to carbohydrate in its utilization per calories.[22, 25] Similar results have been recently obtained in laboratory animals.[13]

BRANCHED-CHAIN AMINO ACIDS. Recent investigations from both this and other laboratories suggest that the branched-chain amino acids may have special properties which are extremely useful in the severely stressed or septic patient: (1) they apparently are oxidized by the peripheral muscle without the intervention of glucose; (2) they serve primarily as substrates for alanine and the glucose alanine cycle; (3) they apparently control, at least in part, both protein synthesis and the flux of amino acids from muscle.[3, 16] In the moderately stressed laboratory animal and in the postoperative patient, the administration of the 3 branched-chain amino acids alone may result in nitrogen equilibrium.[11, 14]

THE CLINICAL USES OF PARENTERAL NUTRITION

In general the clinical usefulness of parenteral nutrition is dependent on the complication rate in that particular institution, i.e., if the complication rate is low then parenteral nutrition will be widely used. In the ideal situation parenteral nutrition would be utilized in all hospitalized patients unable to consume adequate food by mouth. Since eating is a normal function, nutrient intake should continue throughout illness. On the other hand, parenteral nutrition is expensive and potentially dangerous, and to date there are few data addressed to the fact that several days of starvation in an otherwise healthy individual results in any difference in outcome. Thus, any further discussion of parenteral nutrition must take into account the risk as well as the potential benefits to be accrued.

Inability to use the Gut

These remain the principal indications for parenteral nutrition, and include gastrointestinal-cutaneous fistulas, the short bowel syndrome, inflammatory bowel disease, and all other diseases which result in prolonged ileus or inability of the gut to function.

FISTULAS. Fistulas remain the classical indication for parenteral

nutrition in that food increases the output of the fistula. All studies agree that the incidence of spontaneous closure in patients with gastrointestinal cutaneous fistula has increased since the advent of parenteral nutrition. Two large recent series however, question whether mortality has in fact decreased since the institution of parenteral nutrition and credit the decrease in mortality to other earlier parasurgical improvements in intensive care.[30, 33] This obviously is a moot point, as is agreed that total parenteral nutrition is extremely useful in the management of these patients as it encourages spontaneously closure.[30, 33] In those patients in whom spontaneous closure does not occur, the provision of nutrition will enable the patient to come to operation in much better condition.

THE SHORT BOWEL SYNDROME. This usually results either from resection of massive amounts of small bowel secondary to mesenteric thrombosis or repeated resections with inflammatory bowel disease. The gut cannot be utilized even with predigested or elemental diets because of its short length and because the osmotic effects of such diets result in massive diarrhea. Thus, a period of bowel rest, which authorities generally agree should be between 1 and 2 months, with adequate provision of nutrition, will enable the small bowel to hypertrophy; thereafter, many patients will tolerate oral food. It is important that while hypertrophy is proceeding, adequate nutrition must continually be supplied by vein. These patients may be candidates for home parenteral nutrition.

INFLAMMATORY BOWEL DISEASE It is perfectly logical that patients with inflammation of the bowel be given adequate nutrition and the bowel put at complete rest. Numerous studies have now confirmed that apparent benefit of parenteral nutrition in Crohn's disease or regional enteritis.[3] Apparent remission may take place in up to 75 per cent of patients with Crohn's disease confined to the small bowel; these remissions may last as short as 24 hours and as long as 8½ years. What is bothersome is the inability to predict which patients will do well. Numerous doubleblind randomized studies have been attempted; however, since in most patients, medical therapy has failed, it is not quite clear what the control random treatment will be.

Most agree that short term parenteral nutrition is not effective in ulcerative colitis and merely serves as a means of support.[31]

PANCREATITIS. Pancreatitis is associated with disturbances in gut function, often for prolonged periods. Recent studies by Goodgame and Fischer have suggested that even in situations where parenteral nutrition was started as long as 5 days after the attack, when it became clear that the patient's gut function would not return, little effect on the primary disease could be discerned. However, patient support could be provided for prolonged periods of time.[19] Prospective studies in which nutritional support is begun early are clearly needed in order to demonstrate a beneficial effect on the disease process itself.

PROLONGED ILEUS. Respiratory failure, cardiac cachexia and prolonged post-traumatic situations with large losses of lean body mass are all situations where abnormal demands on body protein can be ex-

pected. It is appropriate under these circumstances to begin parenteral nutrition early before too much lean body mass has been lost, as it the author's prejudice that it is much easier to prevent the loss of lean body mass than try and replete it once it has been lost.

Preoperative Use of Parenteral Nutrition

One active area of investigation in parenteral nutrition is the initiation of parenteral nutrition to restore at least some portion of weight lost prior to major surgery. This constitutes a large group of patients. Only one preliminary study has been published in which a trend in the direction of better operative results was seen.[21] Another study appeared to demonstrate that in patients who had lost weight and were anergic to skin recall antigens that a high rate of sepsis, morbidity and/or mortality might be expected.[26] More recent data, especially in patients with neoplastic disease, does not appear to confirm this. The situation appears much more complicated than was initially appreciated, and the interaction between the host, the neoplasm and the state of nutrition all appear to enter into whether such a patient is anergic. It is also not clear what anergy indicates. This area is clearly in need of prospective studies, a large number of which are in progress.

Disturbances in Nitrogen Metabolism

The availability of individual synthetic amino acids makes it possible to vary the amino acid components of nutritional solutions. These second generation solutions have been designed for disease states with disturbances in nitrogen metabolism: renal failure, hepatic failure, and more recently sepsis.

RENAL FAILURE. The metabolic products of protein breakdown are normally converted into urea among other things, but the excretion of urea is hampered by the presence of renal failure. This is even more troublesome because most patients with acute tubular necrosis, at least in the surgical setting, are hypercatabolic either because of their primary disease or because renal failure itself apparently is hypercatabolic. While much waste nitrogen is thus available, it was not clear however how this might be harnessed and "fixed," as it were, to enter into protein synthesis. Giordano[17] and Giovanetti[18] utilized diets which under ordinary circumstances would be considered protein deficient. All essential amino acids were furnished with an adequate amount of energy; nitrogen derived from urea as ammonia in the gut by urease-producing organisms could then be "fixed" into nonessential amino acids by transamination, and, with energy, synthesized for protein. At least this was thought to be the mechanism. Wilmore and Dudrick first reported clinical usefulness of such materials administered as solutions.[6] Abel and co-workers carried out a prospective randomized doubleblind study in a reasonably homogeneous group of patients with acute tubular necrosis.[1] In this study survival was enhanced by the administration of a protein-deficient high calorie intravenous solution consisting only of essential amino acids and 47 per cent hypertonic dextrose,[1] a solution which is now commercially available. It is not

clear that the mechanism is reincorporation of protein, the so-called "Giordano effect," or whether decreased emergence of urea nitrogen is the mechanism by which this operates. Whatever the mechanism, in renal failure, if dialysis does not appear imminent the use of essential amino acids and hypertonic dextrose is appropriate. Once dialysis is on a schedule, both essential and nonessential amino acids are being lost and a more complete solution is necessary. It is not clear that intravenous fat is a suitable caloric source in renal failure.

HEPATIC FAILURE. In an urban setting in which the most common form of liver disease is secondary to alcoholism, patients are usually malnourished, and often enter the hospital with some form of surgical catastrophe. Thus, while these patients require protein for nutritional purposes, they are often intolerant of protein because of hepatic encephalopathy. Space does not permit the details, but the development of an appropriate solution stemmed basically from research which suggested that a disturbance in central neurochemical transmitters was responsible, at least in part, for the cause of hepatic encephalopathy. This alteration in central neurotransmitters could be related to a disturbed plasma amino acid profile, which in turn affected central nervous system neutral amino acids, which are precusors of central neurotransmitters. The studies were undertaken first in animals and then in patients in which the abnormalities in plasma amino acid profile would be corrected by the infusion of amino acid solution rich in branched-chain amino acids and deficient in aromatic amino acids.[9, 10] This solution (F080) has several effects: (1) decreased emergence of aromatic amino acids by decreasing muscle amino acid catabolism; (2) the promotion of positive nitrogen balance and protein synthesis therapy utilizing the aromatic amino acids; (3) competition for entry at the blood brain barrier between the branched-chain amino acids and the toxic aromatic amino acids, and (4) possible changes in the blood brain barrier itself.

Preliminary studies from both this and other laboratories have revealed that this particular solution, either in intravenous or in oral form, is particularly well tolerated and that positive nitrogen balance may be achieved in patients with encephalopathy with infusions of amounts of amino acids up to 80 to 100 gm for 24 hours, with arousal from hepatic encephalopathy.[10]

SEPSIS. Some of the underlying mechanisms responsible for the various metabolic disturbances in hepatic dysfunction also appear to operate in severe overwhelming sepsis. There is failure of energy production, increased glucagon and relatively decreased insulin, as well as decreased production of ketone bodies secondary to early hepatic dysfunction. In a recent study from this laboratory Freund and his coworkers described a disturbed amino acid pattern in sepsis with increased plasma aromatic and sulfur-containing amino acids, normal branched-chain amino acids, and decreased alanine.[15] Furthermore the amino acid pattern appeared to be predictive of mortality. In another group of patients correction of this plasma amino acid abnormality was undertaken by the infusion of a branched-chain enriched

amino acid solution (F080) which appeared to improve mentation and perhaps contributed to a favorable outcome.[6] Further studies are underway but it does not appear that in the severely stressed patient an increased amount of branched-chain amino acids might be useful.

Cancer

The patient with cancer develops cachexia from a number of circumstances including: (1) anorexia, (2) the metabolic demands of the tumor, (3) the therapeutic attempts on the part of physicians to eradicate the tumor (surgery) resulting in further starvation, and (4) the effects of chemotherapy and radiation.

Active investigation is taking place in the field of neoplastic disease to determine whether an adequately nourished patient is better responsive to chemotherapy and to determine whether the application of total parenteral nutrition to patients who are about to undergo various forms of chemotherapy and radiation therapy will prove to be of value.[4, 5] It is probably too preliminary to state anything with certainty, but several comments appear in order: (1) If one is to undertake maximal chemotherapy or radiation therapy in patients who are expected to survive, adequate nutrition must be maintained. (2) Though laboratory studies have not yet demonstrated differential tumor growth as opposed to the host, this specter persists both in experimental animals and man.[34] (3) The relationship between anergy to skin recall antigens and nutrition in patients with neoplastic disease is not one to one. It is clearly a complicated situation in which both the state of nutrition as well as the cancer itself appear to influence the state of immunologic recall. Whether in fact immunologic recall will prove to be an excellent test before complications of neoplastic disease occur is not clear at the present time.

COMPLICATIONS

A great deal of work over the last decade has been directed at minimizing the complications of parenteral nutrition. In general these efforts have been successful and parenteral nutrition is generally safe in institutions in which a great deal of effort has gone into minimizing such complications, which are complications of placement, late technical complications, sepsis, and metabolic complications.

Complications of Placement

These occur less frequently with increased experience of the insertor but even under the best of circumstances a certain number of complications are unavoidable. With the subclavian approach the most frequent complication is laceration of the apex of the lung giving rise to a pneumothorax, rarely a hemopneumothorax. Laceration of the subclavian vein or artery will result in a hemothorax. Other complications include injury to the brachial plexus, and, on the left side, injury to the thoracic duct.

Late Technical Complications

The most common complication is thrombosis, most often bland. It may occur in as many as 5 to 10 per cent of all catheters that are placed. This is at least partially related to the material used. Polyvinyl catheters probably increase the risk for late thrombosis as compared with Silastic catheters.

Sepsis

This is the most feared of all complications. Numerous studies have now demonstrated that most catheter sepsis originates in the skin and the organisms grown down the catheter, infecting the blood or the fibrin sleeve around the catheter. Hematogenous spread and seeding of the catheter may of course occur especially in high grade and sustained bacteremia such as in burns, but are comparatively rare. Most authorities agree poor catheter care results in sepsis and that exemplary catheter care will prevent septic complications.[32]

In general there are two types of sepsis, the first is bacterial involving skin organisms such as Staphylococcus epidermidis, aerobacter, klebsiella and other nosocomial organisms. Most agree that in the presence of a fever spike, removing the catheter without antibiotic therapy is generally sufficient provided a septic thrombophlebitis is not established. If catheter sepsis is neglected and a septic endovasculitis has been established, this should be treated as any other endovasculitis with intravenous antibiotics in high doses for between 2 and 6 weeks.

Fungal septicemia is a more difficult problem. Recent advances in the immunology of Candida including the use of both Candida precipitins and crossed immunoelectrophoresis have made it possible to judge when a patient is infected as opposed to when a patient is merely colonized.[19] Fungal septicemia however demands the abandonment of the central hypertonic glucose technique and the utilization of a peripheral lipid technique, as well as treatment for 6 weeks with some fungicidal agent such as amphotericin B which in itself is extremely nephrotoxic. Fungemia has an unfortunate habit of lying dormant and negative blood cultures may persist for several days until the glucose-rich infusion is started once again, at which point fungemia reappears. A late complication of fungemia is a true mycotic aneurysm of the superior mesenteric artery, in which the organism apparently has a preference for dwelling, and late thrombosis of the superior mesenteric artery.

Metabolic Complications

Glucose

The most common metabolic complications of parenteral nutrition generally involve glucose. Hyperglycemia probably occurs in about 15 per cent of all patients on central amino acid–hypertonic glucose parenteral nutrition. Prominent at risk for this are generally patients

with decreased secretion of insulin, as is pancreatitis, insensitivity to insulin, as in liver disease, and especially sepsis. Emergent hyperglycemia in a patient who has previously been stable often presages clinical sepsis by about 24 hours.

The use of insulin is the key to the treatment of hyperglycemia. Somewhat surprisingly, patients with even juvenile diabetes do not appear to be at as great a risk for hyperglycemia, especially those still capable of some insulin response to amino acids and perhaps because of the intravenous route of glucose administration.

Hyperglycemia sometimes occurs by this is generally the result of a poor regulation of an infusion. Another form of hypoglycemia is that which occurs secondary to endogenous secretion of insulin at high rates of hypertonic glucose amino acid solution. This may be remedied by slowly decreasing the rate of infusion.

Ions and Trace Metals

Most of the other metabolic complications are deficiency states and result from inadequate administration of various micronutrients and trace elements. Thus, hyponatremia, hypokalemia, hypophosphatemia, and hypomagnesemia are all avoidable, provided adequate amounts of these ions are administered. Some of the trace metals are now emerging as important factors in nutrition. Zinc deficiency, largely described in Japan and New Zealand, occurs in patients with gastrointestinal disease with deficient stores of zinc and in whom adequate zinc maintenance is not forthcoming.[24, 35] All that is required on a daily basis is 6 to 20 mg of zinc.

Copper deficiency, which results in a microcytic anemia secondary to poor red cell maturation, has been described in several patients on long term paterteral nutrition.[27, 36] Chromium deficiency, manifested by glucose intolerance, encephalopathy, and neuropathy, also has been described in several patients on long term parenteral nutrition, particularly those who are continually septic. The shortest duration before the emergence of chromium deficiency is approximately 5 months.[12, 23] As time goes on, more rigid criteria for trace metal administration will be necessary.

Vitamins

Vitamin deficiency is rare, provided adequate replacement is given, although vitamin toxicity due to excesses of the fat-soluble vitamins, vitamins A and D, has been reported. Periodic adjustment of the dose results in prevention of this complication.

HOME PARENTERAL NUTRITION

It is no longer a novelty to have a patient on home or outpatient or long term parenteral nutrition. Some units are aggressive in that any patient who is apparently going to require parenteral nutrition for more than 30 days is taken to the operating room and a Broviac-

Scribner catheter or a similar type of catheter is implanted through a branch of the subclavian vein with a long subcutaneous tunnel for overnight or prolonged administration of parenteral nutrition. The principles of this type of parenteral nutrition are the same as the central hypertonic glucose technique except that approximately 2 liters of hypertonic dextrose amino acid solution is administered overnight. The solution is tapered for approximately 2 hours prior to its being discontinued. Fat is administered intravenously where necessary, although most of these patients can take sufficient oral nutrition to prevent essential fatty acid deficiency. A variety of patients are being maintained on home parenteral nutrition, including patients with short bowel syndrome, massive resection, repeated resections for inflammatory bowel disease, radiation enteritis, gut dysfunction, and so forth.

Patients on long term parenteral nutrition must be taught about the technique in its entirety, so that they may deal with the variety of problems as they arise. If catheter care is meticulous the average catheter life is approximately 1 year, with sepsis the most frequent complication necessitating removal.

SUMMARY

As widespread use of parenteral nutrition enters the second decade, it is obvious that a great deal of progress has been made, both as to increasing safety and developing new solutions. There are few hard data in this area, not surprising in so young a field. Prospective studies hopefully will yield definitive results in areas in which such knowledge is lacking. More importantly, better understanding of various disease states will undoubtedly result in the modification of existing solutions to allow for better treatment.

REFERENCES

1. Abel, R. M., Beck, C. H., Jr., Abbott, W. M., et al: Improved survival from acute renal failure following treatment with intravenous essential L-amino acids and glucose. New Engl. J. Med., *288*:695, 1973.
2. Bury, K. D., Grayston, M., and Kanarens, J.: Comparative weight gain in animals receiving total nutrition by either the intravenous or intragastric routes. J. Surg. Res., 1978 (in press).
3. Buse, M. G., and Reid, M.: Leucine, a possible regulator of protein turnover in muscle. J. Clin. Invest., *58*:1215, 1975.
4. Copeland, E. M., MacFadyen, B. V. J., and Dudrick, S. J.: Effect of intravenous hyperalimentation on established delayed hypersensitivity in the cancer patient. Ann. Surg., *184*:60, 1976.
5. Dudrick, S. J., Copeland, E. M., and MacFadyen, B. V.: The nutritional care of the cancer patient. *In* Greep J. M., Soeters, P. B., Wesdorp, R., et al.: Current Concepts in Parenteral Nutrition. The Hague; Martinus Nijhoff, 1977.
6. Dudrick, S. J., Steiger, E., and Long, J. M.: Renal failure in surgical patients: Treatment with intravenous essential amino acids and hypertonic dextrose. Surgery, *68*:180, 1970.
7. Dudrick, S. J., Wilmore, D. W., Vars, H. M., et al.: Can intravenous feeding as a sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann. Surg., *169*:974, 1969.

8. Dudrick, S. J., Wilmore, D. W., Vars, H. M., et al. Long term total parenteral nutrition with growth development and positive nitrogen balance. Surgery, *64*:134, 1968.
9. Fischer, J. E., Funovics, J. M., Aguirre, A., et al.: The role of plasma amino acids in hepatic encephalopathy. Surgery, *78*:276, 1975.
10. Fischer, J. E., Rosen, H. M., Ebeid, A. M., et al.: The effect of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery, *80*:77, 1976.
11. Freund, H., Yoshimura, N., Lunetta, L., et al.: The role of the branched chain amino acids in decreasing muscle catabolism. Surgery, *83*:611, 1978.
12. Freund, H., Atamian, S., and Fischer, J. E.: Chromium deficiency during total parenteral nutrition. J.A.M.A.,*241*:496, 1979.
13. Freund, H., and Fischer, J. E.: Effects of fat and glucose with and without amino acids. Surg. Forum, in press.
14. Freund, H., Hoover, H., Atamian, S., et al.: Infusion of the branched chain amino acids on post-operative patients: Anticatabolic properties. Ann. Surg., in press 1979.
15. Freund, J., Ryan, J. A., and Fischer, J. E.: Amino acid derangements in patients with overwhelming sepsis: Treatment with branched chain amino acid rich infusions. Ann. Surg., *188*:423-430, 1978.
16. Fulkes, R. M., Li, J. B., and Goldberg, A. L.: Effects of insulin, glucose and amino acids on rat turnover in rat diaphragm.
17. Giordano, C.: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. J. Lab. Clin. Med., 62:231, 1963.
18. Giovannetti, S., and Maggiore, Q.: A low-nitrogen diet with protein of high biological value for severe chronic uraemia. Lancet, *1*:1000, 1964.
19. Glew, R. H., Buckley, H. R., Rosen, H. M., et al.: Serologic tests in the diagnosis of systemic candidiasis. Enhanced diagnostic accuracy with crossed immunoelectrophoresis. Amer. J. Med., *64*:586, 1978.
20. Goodgame, T. J., and Fischer, J. E.: Parenteral nutrition in the treatment of acute pancreatitis: Effect on complications and mortality. Ann. Surg., *186*:651, 1977.
21. Holter, A. R., and Fischer, J. E.: The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. J. Surg. Res., 23:31, 1977.
22. Jeejeebhoy, K. N., Anderson, G. M., and Nakhooda, K. N.: Metabolic studies in total parenteral nutrition with lipid in man, comparison with glucose. J. Clin. Invest., 57:125, 1976.
23. Jeejeebhoy, K. N., Langer, B., Tsallas, G., et al.: Total parenteral nutrition at home: Studies in patients surviving 4 months to 5 years. Gastroenterology, *71*:943, 1976.
24. Kay, R. G., Tasman-Jones, C., Pybus, J., et al.: A syndrome of acute zinc deficiency during total parenteral nutrition in man. Ann. Surg., *183*:331, 1976.
25. Long, J. M., III, Wilmore, D. W., Mason, A. D., et al.: Comparison of carbohydrate and fat as caloric sources. Surg. Forum, *26*:108. 1975.
26. Meakins, J. L., Pietsch, J. B., Bubenick, O., et at.: Delayed hypersensitivity: Indicator of acquired failure of host defenses in sepsis and trauma. Ann. Surg., *186*:241, 1977.
27. Palmisano, D. J.: Nutrient deficiencies after intensive parenteral alimentation. New Engl. J. Med., *291*:799, 1974.
28. Peters, C. A., and Fischer, J. E.: Calorie nitrogen ratio in parenteral nutrition. J. Surg. Res., 22:521, 1977.
29. Piccone, V., and Leveen, H.: Results of esophagogastrectomy for carcinoma of the esophagus. Presented at the Society for Thoracic Surgeons, January 1979.
30. Reber, M. A., Roberts, C., Way, L. W., et al.: Management of external gastrointestinal fistulas. Ann. Surg., *188*:460-467, 1978.
31. Reilly, J., Ryan, J. A., Strole, W., et at.: Hyperalimentation in inflammatory bowel disease. Amer. J. Surg., *131*:192, 1976.
32. Ryan, J. A., Abel, R. M., Abbott, W. M., et al.: Complications in total parenteral nutrition: A prospective study of 200 consecutive patients, New Engl. J. Med., *290*:757, 1974.
33. Soeters, P. B., and Fischer, J. E.: Gastrointestinal cutaneous fistula: Review of 404 cases. Submitted for publication.
34. Steiger, E., Oram-Smith, J., Miller, W., et al.: Effects of nutrition on tumor growth and tolerance of chemotherapy, J. Surg, Res., *18*:455, 1975.
35. Takagi, Y., Itakura, R., Okada, A., et al.: A clinical analysis of zinc dificiency during total parenteral alimentation in man. Japanese Journal of Surgery, *33*:427, 1975.
36. Vilter, R. W., Bozian, R. C., Hess, E. V., et al.: Manifestations of copper deficiency in a patient with systemic sclerosis on intravenous hyperalimentation. New Engl. J. Med., *291*:188, 1974.
37. Wretlind, A.: Complete intravenous nutrition: Theoretical and experimental background. Nutr. Metab. (Suppl.). *14*:1, 1972.

University of Cincinnati Medicine Center
Cincinnati, Ohio 45267

Interactions Between Drugs and Nutrients

*Daphne A. Roe, M.D.**

Nutrient and non-nutrient constituents of foods and beverages can interact with drugs such that the predictable effect of the drug is modified. Outcome of drug-food, drug-alcohol, and drug-nutrient interactions include a change in the rate or level of drug absorption, change in the rate of drug metabolism, drug-food or drug-alcohol incompatibilities, as well as drug-induced nutritional deficiencies. Megadoses of vitamins can alter drug responsiveness. Nutrients, particularly vitamins, can be used as drugs, not only in the treatment of nutritional deficiency disease, but also for their pharmacological effects in disorders that may not be due to nutritional factors.

EFFECTS OF FOOD ON DRUGS

Effects of Food on Drug Absorption and Bioavailability

Absorption of drugs may be increased or decreased by physiological changes which occur in the gastrointestinal tract in the fed versus the fasting state.[122] Nutrients in foods can promote drug absorption. Non-nutrient components of the diet, including specific forms of dietary fiber, may adsorb drugs, producing a transient or net reduction in drug absorption. Delayed absorption of common drugs such as digoxin occurs when the drug is taken at the same time as food. Delayed absorption of drugs, brought about by food, does not imply that less drug is totally absorbed, but rather that the time for a drug to reach peak blood levels after a single dose is lengthened.[62] Little is known about the specific components of food which delay drug absorption. Studies do indicate that the delaying effect of food on absorption of acetaminophen may be due to the pectin content.[50] Reduced absorption of drugs may be due to eating at the same time or close to the time

*Professor of Nutrition, Division of Nutritional Sciences, Cornell University, Physician, Tomkins County Hospital, Ithaca, New York

when the drug is taken.[57] Drugs which are more slowly or less efficiently absorbed when taken with food are shown in Table 1. The absorption of other drugs such as nitrofurantoin, hydrochlorothiazide, and griseofulvin is promoted by food intake. Drugs and nutrients which are better absorbed after food are griseofulvin,[23] nitrofurantoin,[6] riboflavin,[59] riboflavin-5′-phosphate,[52] propranolol,[72] metoprolol,[72] hydralazine,[70] spironolactone,[71] carbamazepine,[60] and propoxyphene.[124] Known mechanisms whereby food or nutrients promote drug absorption or bioavailability are as follows.

1. Food enhances absorption of dosage forms of drugs with the poorest in vitro dissolution characteristics. It is believed that delayed gastric emptying time caused by the presence of food in the stomach allows for disintegration and dissolution of these drug formulations.[55] On the other hand, macrocrystalline nitrofurantoin in capsule form is much better absorbed after food and it is believed that this is a specific example of a drug requiring prolonged residence in the stomach for dissolution.[6]

2. Delayed gastric emptying time may allow metering out of a drug (or nutrient) solution from the stomach to the optimal saturable absorption site in the small intestine. It has been demonstrated that absorption of riboflavin or riboflavin-5′-phosphate is enhanced by intake of food,[52, 59] particularly of food containing fiber,[103] and also by intake of carbonated beverages.[48] The latter effect has been attributed to a decrease of gastric emptying rates induced by carbohydrates (sugar) and phosphoric acid present in the beverage. It has been suggested that it may be through this mechanism that food promotes absorption

Table 1. *Drugs for Which Absorption is Delayed or Reduced by Food**

DELAYED	REDUCED
Amoxicillin	Penicillin G
Cephalexin	Penicillin V (K)
Cephradine	Phenethicillin
Sulfanilamide	Ampicillin
Sulfadiazine	Amoxicillin
Sulfamethoxine	Tetracycline
Sulfamethoxypyridazine	Demethylchlortetracycline
Sulfisoxazole	Methacycline
Sulfasymazine	Oxytetracycline
Aspirin	Aspirin
Acetaminophen†	Propantheline
Digoxin	Levodopa
Furosemide	Rifampicin
Potassium ion	Doxycycline
	Isoniazid
	Phenobarbital

*References 9, 21, 22, 37–39, 55, 61, 62, 79, 108, 115, 123

†Probable pectin effect

of drugs such as hydrochlorothiazide.[49] The absorption of propoxyphene is better after a carbohydrate meal (this may also be an effect of gastric emptying time).[124]

3. Nutrients may promote drug absorption. The antifungal agent, griseofulvin, is better absorbed when taken with a meal containing fat, probably because it is a lipid-soluble drug and because bile flow may enhance absorption. Therapeutic diets may produce or alter the efficiency of griseofulvin absorption. For example, low fat diets prescribed for patients with hyperlipidemia, atherosclerotic heart disease, and diabetes mellitus may significantly reduce the absorption of griseofulvin. When low fat diets have been prescribed and it is necessary to administer griseofulvin, then a micronized or ultramicronized form of the drug should be used, or it should be given in suspension in a small volume of corn oil.

4. Food increases splanchnic blood flow and hence enhances drug absorption.[65]

5. Food enhances the bioavailability of certain drugs. Oral bioavailability of a drug is defined as the fraction of unchanged drug reaching the systemic circulation after oral intake compared to that following intravenous administration. Melander[69] has suggested that since absorption of both propranolol and metaprolol is complete under fasting condition, food (or food components) cannot actually promote absorption but that food intake may reduce first pass extraction and hence hepatic metabolism of these drugs.

Absorption of ethanol from alcoholic beverages is slowed by intake with food.[109] The tradition of drinking milk before liquor or other alcoholic beverages has a sound physiological basis.[73] The delaying effect of food on ethanol absorption may be explained by slower absorption of ethanol via the gastric absorption site because of altered diffusion rate in a filled stomach, and delayed gastric emptying so that less alcohol reaches the area of maximal absorption in the small intestine.

Alcohol taken with slow-release drug formulations may produce untoward effects. For example, if alcoholic beverages are drunk at or close to the same time that slow-release antihistamine capsules are taken, dissolution of the preparation is more rapid than intended, and the patient may rapidly become somnolent. Patients who are not appraised of this effect could be involved in auto accidents when falling asleep at the wheel of the vehicle.[89]

Diet and Drug Metabolism

In animals as well as in human studies, it has been shown that changes in diet may affect the rate of drug metabolism. Drugs may be metabolized faster when patients are on high protein-low carbohydrate diets rather than high carbohydrate-low protein diets. Kappas et al.[53] reported that change in the ratio of carbohydrate to protein in the diet can alter the elimination rate of model drugs including antipyrine and theophylline.

Indolic compounds present in cabbage and Brussels sprouts can speed up the rate of drug metabolism.[85] Cooking methods may also alter the rate of drug metabolism. Charcoal-broiling promotes hepatic drug metabolism.[54]

Changes in the intestinal microflora produced by diet, as for example, alterations in dietary fiber source or level or change in the level of dietary protein, may influence intestinal drug metabolism.[107]

ADVERSE DRUG REACTIONS CAUSED BY FOOD

Adverse reactions to drugs can be precipitated by intake with specific foods or alcoholic beverages. Reactions vary greatly in intensity, some being unpleasant enough to prevent the person from wishing to go through the episode again, while other reactions are life-threatening. The major types of drug-food and drug-alcohol incompatibilities are summarized in Table 2.

Table 2. *Drug-Food and Drug-Alcohol Incompatibilities*

CLASSIFICATION	REACTANTS		EFFECT
	1	2	
1. Tyramine reactions	*MAO Inhibitors*	*High tyramine/ dopamine foods*	
	Antidepressants, e.g., phenelzine Procarbazine Isoniazid (INH, Isonicotinic acid hydrazide)	Cheese Red wines Chicken's liver Broad beans Yeast extracts	Flushing Hypertension Cerebrovascular accidents
2. Disulfiram reactions	*Aldehyde dehydrogenase inhibitors*	*Ethanol*	
	Disulfiram (Antabuse) Calcium carbimide Metronidazole Nitrofurantoin C. atramentarius* Sulfonylureas	Beer Wine Liquor Foods containing alcohol	Flushing, headache Nausea, vomiting Chest and abdominal pain
3. Hypoglycemic reactions	*Insulin releasers*	*Ethanol*	
	Oral hypoglycemic agents Sugar (as in sweet mixes)		Weakness Mental confusion Irrational behavior Loss of consciousness
4. Flush reactions [see 2]	*Miscellaneous*	*Ethanol*	
	Chlorpropamide [+ diabetes] Griseofulvin Tetrachlorethylene		Flush Dyspnea Headache

*Coprinus atramentarius = Inky cap mushroom.

Tyramine Reactions

Tyramine reactions have been recognized since 1961 when it was first observed that patients receiving drugs which are monamine oxidase inhibitors may develop acute hypertensive attacks.[99] Monamine oxidase inhibitor drugs presently available in the United States include phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate). These drugs were introduced into therapeutic use as mood elevating agents for the treatment of severe depression.[42] Whereas use is now limited by knowledge of potential side effects, monamine oxidase inhibitor drugs are presently recommended for the treatment of selected patients with psychotic depression and patients with phobic anxiety. These drugs elevate levels of norepinephrine and serotonin in the central nervous system and potentiate the cardiovascular effect of simple phenylethylamines such as tyramine.[30] Asatoor et al.[4] not only showed that toxic reactions might occur when cheese was eaten by patients on these drugs, but also observed that the reactions resembled those associated with paroxysmal release of catecholamines from a pheochromocytoma. The attacks are characterized by hypertension of short duration, headaches, palpitations, nausea, and vomiting. In some instances, major cerebrovascular accidents have been documented. The severity of the attack has been related both to drug dosage and also to the level of tyramine in particular foods or food samples. Foods which have been demonstrated to cause hypertensive crises in patients receiving monamine oxidase inhibitor drugs are those high in tyramine or in dopamine.[11, 45, 83]

Cheeses which have been allowed to mature have a high tyramine content. Intake of unmatured cheeses by people receiving these drugs offers a much lower risk of tyramine reactions and may be entirely innocuous. Blackwell and Mabbit measured the tyramine content of a number of cheeses and found the highest values among cheddar cheeses for those with acid or rancid flavors.[10]

Other foods and beverages which have been shown to produce hypertensive attacks in patients on monamine oxidase inhibitor drugs are pickled herring, chicken livers, broad beans, Chianti wines, and beers.[47] In broad beans, the amino acid dopa or its amine derivative dopamine triggers attacks.[12] Both tyramine and dopa, or dopamine, which escape oxidative deamination, are believed to enter the systemic circulation, release norepinephrine from local stores in nerve endings, and so prolong the action of this catecholamine on adrenergic receptors. These drugs inhibit monamine oxidase either in the intestine or in the liver, or in both of these sites. Reactions usually occur within 30 to 60 minutes after ingestion of the particular food or beverage.[66]

The interaction between tranylcypromine and cheddar cheese has actually been utilized to treat patients with severe postural hypertension. When this drug was given at a dose of 70 mg per day and 90 gm of cheddar cheese, equivalent to 26 mg of tyramine per day, was also given daily, the blood pressure in a hypotensive patient rose so that she was able to stand up without developing symptoms.[28] The tyra-

mine content of foods which commonly evoke hypertensive tyramine reactions are shown in Table 3.

Other monamine oxidase inhibitor drugs which may evoke a tyramine reaction are used for quite other therapeutic purposes than the treatment of depression. Kent Smith and Durack[56] reported tyramine reactions from ingestion of cheese with isoniazid. Procarbazine, used in the treatment of Hodgkin's disease, is a mild monamine oxidase inhibitor and is also capable of causing hypertensive attacks when taken with foods containing high levels of tyramine.[116]

Table 3. *Tyramine Content of Foods and Beverages**

FOODS/BEVERAGES	TYRAMINE CONTENT (μg/g)
Cheese	
Cheddar	120–1500
Camembert	20–2000
Emmenthaler	225–1000
Stilton	466–2170
Processed	26–50
Brie	0–200
Gruyere	516
Gouda	20
Brick, natural	524
Mozzarella	410
Roquefort	27–520
Parmesan	4–290
Romano	238
Provolone	38
Cottage	5
Fish	
Salted, dried	0–470
Pickled herring	3000
Meat	
Meat extracts	95–304
Beef liver (stored)	274
Chicken liver (stored)	100
Vegetables	
Avocado	23
Fruit	
Banana	7
Alcoholic Beverages	
Beer and ale	1.8–11.2
Wines	0–25
Chianti	25.4
Sherry	3.6

*Adapted from Lovenberg, W.: Some vaso- and psychoactive substances in food. *In* Natural Toxicants in Food. National Academy of Science, Washington, D.C., 1973, Table 1, p. 172, Table 2, p. 174.

Disulfiram Reactions

The acute reactions which occur when people receiving the drug disulfiram (Antabuse) drink alcoholic beverages or consume foods containing alcohol begin about 15 minutes after the alcohol-containing food or drink is taken. Flushing and headache are followed by nausea, vomiting, and a variable degree of chest and/or abdominal pain. Symptoms are very unpleasant, and the drug has therefore come to be used as a deterrent to drinking for alcoholics. Disulfiram reactions are caused by drugs that are aldehyde dehydrogenase inhibitors. Drugs, other than disulfiram (Antabuse) itself, which have been documented as causing disulfiram reactions, are: calcium carbimide, used in Canada as an aversive drug for alcoholics; metronidazole, chlorpropamide, furazolidone, griseofulvin, quinacrine, tolazoline, and procarbazine.[35, 42, 76, 88, 110] The inky cap mushroom *Coprinus atramentarius* contains an aldehyde dehydrogenase inhibitor. When these mushrooms are eaten with or followed by alcoholic beverages, including beer, disulfiram reaction occurs.[15, 96]

Hypoglycemic Reactions

Drugs and/or foods having the property of inducing rapid release of insulin can cause hypoglycemia when taken with alcoholic beverages. Thus hypoglycemia may develop when diabetic patients receiving oral hypoglycemic agents ingest alcohol. Reactions are characterized by weakness, mental confusion, irrational behavior and, if untreated, loss of consciousness. Milder hypoglycemic reactions have been identified when sweet or semi-sweet drinks such as gin and tonic are ingested on an empty stomach. A warning has been given that hypoglycemic attacks following the drinking of alcohol with sweet mixes in the fasting state could very easily lead to automobile accidents.[84]

Flush Reactions

Flush reactions have been described when patients on a variety of drugs also have a drink of a beverage containing alcohol. The flushing appears rapidly after ingestion of the drink and may be accompanied by dyspnea and headache. Chlorpropamide is known to induce the flush reaction in certain diabetics. Pike and Leslie[93] have described a distinctive syndrome in diabetics or prediabetics, inherited as an autosomal dominant trait, which is associated with chlorpropamide-alcohol flush reaction. These authors have found that this syndrome can be detected with a single dose of chlorpropamide before the onset of glucose intolerance and that therefore a "flushing test" could be used as a genetic marker for the syndrome.

Other drugs which may induce a flush reaction are griseofulvin, in which the reaction is usually confined to the period soon after the initiation of treatment, and tetrachlorethylene. The etiology of the griseofulvin and tetrachlorethylene flush reactions is not well understood. Tetrachlorethylene also potentiates the sedative effects of alcohol.[61]

When central nervous system depressant drugs including hypnotic

sedatives, antihistamines, phenothiazines, and narcotic analgesics are taken with alcoholic beverages, drug effects which may cause loss of consciousness are potentiated.[110]

EFFECTS OF DRUGS ON FOOD INTAKE AND ABSORPTION OF NUTRIENTS

EFFECTS OF DRUGS ON APPETITE, FOOD INTAKE, AND BODY WEIGHT

Numerous drugs in common therapeutic use alter appetite. Drugs which promote appetite may be used intentionally for this purpose, or enhanced desire for food in general or for certain foods may be considered as an undesirable side effect of such drugs. Despite the obvious connection between stimulation of appetite, increased food intake and weight gain, these causal associations cannot be assumed.

Hyperphagic Agents

ANTIHISTAMINES. Appetite can be stimulated intentionally in debilitated children or adults by administration of cyproheptadine hydrochloride (Periactin), which is both an antihistamine and a serotonin antagonist. Increased hunger with administration of cyproheptadine occurs largely when anorexia previously existed. Cyproheptadine may be considered as a rational therapy for treatment of anorexia except when distaste for food is associated with weight phobia (as in anorexia nervosa) or with disease in which food intake causes pain or discomfort.[30] Asthmatic children treated with cyproheptadine experience increased appetite and gain weight.[8] Cyproheptadine has also been shown to improve appetite and cause significant weight gain in underweight adults.[117] Mainguet[64] also found that cyproheptadine is a nontoxic appetite stimulant.

PSYCHOTROPIC DRUGS. Appetite promoting effects of psychotropic drugs have been recognized, particularly in psychiatric patients on prolonged high hosage therapies.[86] Chlorpromazine (Thorazine) and other phenothiazines can improve appetite in agitated patients. Benzodiazepines including chlordiazepoxide (Librium) and diazepam (Valium) stimulate appetite and increase food intake, both in people and in experimental animals. In rats it has been demonstrated that diazepam promotes food intake under conditions of conflict and it has been hypothesized that this may also be the case in human subjects.[51] Meprobamate has appetite-stimulating properties when given to disturbed patients. Hydroxyzine hydrochloride (Atarax, Vistaril), a mild tranquilizer with antiemetic and antihistaminic properties, may also increase the desire for food. Patients with long-standing dermatoses are particularly likely to experience increased appetite with intake of hydroxyzine, probably because of associated relief from itching (personal observation).

Whereas tranquilizers given to disturbed psychotic patients often effect a marked increase in food intake such that patients become obese, these same drugs given to geriatric patients may have an oppo-

site effect. When phenothiazines or benzodiazepines are given in high dosages to elderly patients whose rate of drug metabolism is slowed, somnolence and disinterest in food, as well as in surroundings in general, may be responsible for diminished food intake.

Tricyclic antidepressants, like the tranquilizers, may promote appetite. Specific drugs in this class are recognized as having a very marked effect on the desire for food. Amitriptyline (Elavil) increases appetite and food intake and may cause massive weight gain.[3] Patients receiving this drug often describe a craving for sweets.[87] Combined tricyclic and monamine oxidase inhibitor antidepressants have been found to induce weight gain in a high percentage of patients with depressive illness.[37a]

Tranquilizers such as chlorpromazine have been used in the management of anorexia nervosa. However, it is to be questioned whether the beneficial effects of the drug on the disease result from stimulation of appetite. Evidence suggests that chlorpromazine given to patients with anorexia nervosa may reduce resistance to counseling.[20a]

Hypoglycemic Agents

In diabetics and nondiabetics, injections of insulin in the fasting state induce a sensation of hunger. Insulin-induced hypoglycemia, however, may be associated with nausea and a sensation of weakness, rather than a desire for food. The sulfonylurea tolbutamide and chlorpropamide increase appetite in certain diabetic patients, and may induce weight gain. Pawan has suggested that these drugs may stimulate appetite through pancreatic release of insulin.[86]

Steroids

Anabolic steroids including methandrostenolone (Dianabol), nandrolone phenproprionate (Durabolin), and norethandrolone (Nilevar) increase appetite in debilitated patients. Appetite may also be stimulated by testosterone. Weight gain associated with administration of these drugs promotes nitrogen retention with increase in lean body mass.

Glucocorticoids may stimulate appetite, leading to weight gain. The appetite-stimulating effects of glucocorticoids are most notable in patients with chronic adrenal insufficiency or anterior pituitary insufficiency. When corticosteroids are used in the treatment of leukemia, appetite and weight gain improve only if the appetite depressant effects of chemotherapeutic drugs such as methotrexate do not outweigh the effects of the glucocorticoids.

Increased appetite with improved food intake and weight gain may occur with administration of anti-infective drugs, particularly tuberculostatic drugs in tuberculosis. Altered responsiveness to food under these circumstances is a sign of improved well-being.[86]

Hypophagic Agents

AMPHETAMINES AND RELATED STIMULANT DRUGS. Unsubstituted amphetamines and related drugs have been and are still used as anorectic agents in the treatment of obesity. Alteration of appetite by un-

substituted amphetamines may be due to catecholamine-dependent mechanisms.[13] In obese people, anorectic effects of these drugs are significant on initial administration. However, for chronic management of obesity, these drugs are unsatisfactory, both because of adverse side effects and because efficacy in reducing body weight is limited since hyperphagic obese people tend to eat in response to sensory appeal of food rather than in response to appetite.[74, 119]

Fenfluramine (Pondimin), a trifluoromethyl-substituted amphetamine which is also widely used as an appetite suppressant, has a central effect which occurs through activity of the drug on serotonin-dependent pathways.[25]

Hyperactive children receiving amphetamines such as dextroamphetamine or the related stimulant drug, methylphenidate, exhibit growth retardation. Slow weight gain and height gain is associated with diminished food intake. Effects are dose-dependent. When these drugs are discontinued in these children, growth rebound occurs and is proportional to the previous growth depressant. It is believed that the growth rebound is associated with increase in food intake.[104-106]

Cancer Chemotherapeutic Drugs

Antineoplastic drugs including methotrexate as well as purine and pyrimidine derivatives frequently induce anorexia as well as nausea and vomiting in cancer patients. Aversions to food, particularly to meat, may arise as a result of the primary disease or may be associated with the chemotherapy. In children with leukemia it has been shown that foods given during the period of chemotherapy may become distasteful. Anorexia followed by return of appetite occurs with antileukemia multidrug regimens. Methotrexate, particularly when given when the patient is in relapse, will frequently cause anorexia in association with adverse gastrointestinal symptoms. Administration of corticosteroids with this regimen may promote appetite. Abnormalities in taste including aversion to meat associated with the presence of malignant primary or secondary neoplasms may be normalized by cancer chemotherapeutic agents.[27, 75]

Other Agents

CHELATING AGENTS. D-Penicillamine, used in the treatment of Wilson's disease, cystinuria, heavy metal poisoning, and rheumatoid arthritis, may produce loss of taste. Loss of taste is most likely to occur in patients who are receiving this drug for a prolonged period of time, as is the case with penicillamine management of rheumatoid arthritis. Loss of taste has been attributed to zinc deficiency, which is induced by the drug. Recent studies indicate that copper deficiency may be a contributory factor. Loss of taste in these patients is frequently associated with diminished food intake and weight loss.[63]

ALCOHOL. Alcohol abuse can cause anorexia and diminished food intake. Causes of anorexia in alcoholics are inebriation, gastritis, lactose intolerance, pancreatitis, hepatitis, cirrhosis, ketoacidosis, alcoholic brain syndromes, and withdrawal syndromes. Anorexia in alco-

holics can also be due to thiamine deficiency, zinc deficiency, or protein deficiency.[97]

Bulking Agents. Methyl cellulose and guar gum have been shown to reduce food intake if given to healthy normal weight volunteers.[33] These agents, however, offer little for the management of obesity.

Cardiac Glycosides. Digitalis and related cardiac glycosides in high dosage produce anorexia which is usually accompanied by nausea. Vomiting may occur. Digitalis cachexia may result from intoxication with these drugs and mimics cachexia associated with internal malignancy. Rapid return of appetite occurs when drug dosage is adjusted.[5]

Effects of Drugs on Absorption of Nutrients

Drugs Which Promote Absorption of Nutrients

Cimetidine, a potent gastric antisecretory drug, has been shown to be effective in controlling malabsorption and maldigestion associated with the short bowel syndrome. Among patients with this syndrome, those responding to cimetidine have been persons who shortly after massive bowel resection develop maldigestion and malabsorption in association with increased duodenal acid and high volume loads. These pathophysiological changes may impair digestion and absorption in the proximal intestine. High fecal nitrogen losses, steatorrhea, and diarrhea associated with impaired protein and carbohydrate absorption, as well as malabsorption of other nutrients, ensue. Cimetidine has been shown in these patients to reduce gastric acid output, to reduce gastric volume output, to lower duodenal acid load and volume, to prevent a fall in jejunal pH, and to reduce jejunal flow, to decrease fecal fat and nitrogen, as well as fecal volume, and to improve absorption of protein and carbohydrate.[18, 34, 77]

Drugs Which Decrease Absorption of Nutrients

Numerous drugs have been shown to induce malabsorption, which may be primary or secondary. Primary drug-induced malabsorption is here defined as being due to the direct effects of a pharmacologic agent on luminal events or on the intestinal mucosa. Secondary malabsorption occurs when a drug interferes with the absorption, disposition, or metabolism of one nutrient, which in turn leads to malabsorption and deficiency of another nutrient.

Causes and consequences of primary drug-induced malabsorption are summarized in Table 4.

Drugs which cause secondary malabsorption are those which (a) suppress vitamin D absorption or metabolism, leading to malabsorption of calcium; and (b) cause malabsorption or impair utilization of folacin and malabsorption of other nutrients. Chesney et al.[16] found that serum concentrations of 1,25-dihydroxycholecalciferol were

Table 4. *Primary Intestinal Absorptive Defects Caused by Drugs**

DRUG	USAGE	MALABSORPTION OR FECAL NUTRIENT LOSS	MECHANISM
Mineral oil	Laxative	Carotene, vitamins A, D, K	Physical barrier, nutrients dissolve in mineral oil and are lost; micelle formation decreased
Phenolphthalein	Laxative	Vitamin D, Ca	Intestinal hurry; K depletion; loss of structural integrity
Neomycin	Antibiotic to "sterilize" gut	Fat, nitrogen, Na, K, Ca, Fe, lactose, sucrose, vitamin B_{12}	Structural defect; pancreatic lipase lowered; binding of bile acids (salts)
Cholestyramine	Hypocholesterolemic agent; bile acid sequestrant	Fat, vitamins A, K, B_{12}, D, Fe	Binding of bile acids (salts) and nutrients, e.g., Fe
Potassium chloride	Potassium repletion	Vitamin B_{12}	Ileal pH lowered
Colchicine	Anti-inflammatory agent in gout	Fat, carotene, Na, K, vitamin B_{12}, lactose	Mitotic arrest; structural defect; enzyme damage
Biguanides: Metformin Phenformin	Hypoglycemic agents (in diabetes)	Vitamin B_{12}	Competitive inhibition of B_{12} absorption
Para-amino salicylic acid	Anti-tuberculosis agent	Fat, folacin, vitamin B_{12}	Mucosal block in B_{12} uptake
Salicylazosulfapyridine (Azulfidine)	Anti-inflammatory agent in ulcerative colitis, and regional enteritis	Folacin	Mucosal block in folate uptake
Methyldopa	Antihypertensive agent	Folacin, vitamin B_{12}, iron	Autoimmune mechanism?

*Adapted from Roe, D. A.: Effects of drugs on nutrition. Minireview. Life Sciences, *15*:1219–1234, 1974.

reduced in children who were being treated with a corticosteroid (prednisone) for renal disease. Other children with renal disease who were not receiving corticosteroids had normal serum 1,25-dihydroxycholecalciferol levels. Effects were dose-dependent and there was a relationship between the decrease in serum 1,25-dihydroxycholecalciferol levels and the amount of corticosteroid given. These effects could partially explain steroid-induced osteopenia. It was

suggested that steroid-induced osteopenia has several etiologic components, among which the reduced serum level of the renal vitamin D metabolite may be most significant. No explanations of the steroid-induced fall in 1,25-$(OH)_2$-D_3-dihydroxycholecalciferol is presently available.[16]

Drugs commonly causing secondary malabsorption, together with their known or proposed mode of action and nutritional consequences, are listed in Table 5. Both primary and secondary drug-induced malabsorption are due to intraluminal events which inhibit digestion. Drug-induced malabsorption is reversible. A recently described cause of reversible malabsorption is that associated with intake of methyldopa. Intestinal villous atrophy and inflammatory changes in the gut wall were seen in a jejunal biopsy specimen. It was suggested that these changes could be due to an immune mechanism similar to that causing hemolytic anemia and cirrhosis with methyldopa "hypersensitivity." However, the Coombs' test was negative, and the hypothesis was therefore not supported.[114]

Supportive evidence that nutrient malabsorption induced by a drug can produce malabsorption of other nutrients is from reports of methotrexate-induced malabsorption found in children with acute lymphoblastic leukemia. A significant degree of malabsorption has been found in children who had had methotrexate within the previous seven days and the degree of malabsorption is dose-dependent over time. Methotrexate, which functions as an anti-folate drug, impairs intestinal absorption of calcium.[19]

Role of Drugs in Mineral Depletion

Mineral depletion or deficiency may be induced by drugs of varying therapeutic and social use (Table 6). Drugs may induce renal hy-

Table 5. *Drugs Causing Secondary Malabsorption**

DRUG	USAGE	MALABSORPTION	MECHANISM
Prednisone (other glucocorticoids)	Used in allergic and collagen	Calcium	Calcium transport ↓
Phenobarbital	Anticonvulsant	Calcium	Accelerated metabolism of vitamin D
Diphenylhydantoin	Anticonvulsant	Calcium	
Primidone	Anticonvulsant	Calcium	
Glutethimide	Sedative	Calcium	Impaired Ca transport
Diphosphonates	Paget's disease	Calcium	1,25-$(OH)_2$-D_3 formation ↓
Methotrexate	Leukemia	Calcium	Acute folacin deficiency

Adapted from Roe, D. A.: Effects of drugs on nutrition. Minireview. Life Sciences, *15*:1219–1234, 1974.

Table 6. *Mineral Depletion Induced by Drugs*

Diuretics	Calcium (not thiazides) Potassium Magnesium Zinc
Laxatives (Laxative abuse)	Potassium Calcium
Glucocorticoids	Calcium Potassium
Chelating agents (penicillamine)	Zinc Copper
Ethanol	Potassium Magnesium Zinc
Antacids	Phosphates
Non-narcotic analgesics (aspirin, indomethacin)	Iron (by GI blood loss)

perexcretion of minerals or minerals may be lost via the gastrointestinal tract. Whereas diuretics are intentionally used for removal of sodium, diuretic-induced loss of other minerals may be considered as an undesirable side-effect. Oral diuretics such as furosemide, ethacrynic acid, and triamterene cause significant hypercalciuria. Renal clearance of calcium is increased by intravenous furosemide, intravenous ethacrynic acid, or oral triamterene. Oral furosemide decreases the renal tubular reabsorption of calcium and indeed this drug has been used as a temporary measure to control symptoms of hypocalcemia. Thiazide drugs, on the other hand, may cause a transient hypercalcemia.[31, 118]

Potassium depletion is a special risk with prolonged or high dosages of oral diuretics including thiazides, furosemide, and ethacrynic acid. Triamterene and spironolactone are potassium-sparing diuretics. Potassium depletion also occurs with laxative abuse because large amounts of potassium are lost into the lumen of the large intestine. Body deficits of potassium are reflected by hypokalemia. Drug-induced causes of hypokalemia, in addition to diuretics and laxatives, include antibiotics (carbenicillin and penicillin), glucocorticoids, outdated tetracycline which is nephrotoxic, and licorice.[78]

Factitious hypokalemia can occur by self-administration of diuretics, laxatives, and licorice, as well as self-induced vomiting. Persons who induce hypokalemia by these means usually have underlying psychiatric problems such as anorexia nervosa.[36]

Potassium deficiency is manifested by weakness, anorexia, nausea, vomiting, listlessness, apprehension, sometimes diffuse pain, drowsiness, stupor, and irrational behavior. However, marked hypoka-

lemia can occur without abnormal clinical findings. In the elderly, clinical signs may be limited to muscle weakness and electrocardiographic changes.[125] In elderly patients, potassium depletion and hypokalemia are commonly the result of low potassium intake, renal wasting of potassium by use of diuretics, and gastrointestinal loss of potassium by misuse of laxatives. Potassium depletion sensitizes patients to digitalis intoxication. Potassium deficiency also causes structural and functional impairment of the kidney.

Magnesium and zinc are hyperexcreted by patients on oral diuretics as well as by those receiving cardiac glycosides. There has been some debate as to whether the magnesium and zinc deficiencies induced by these drugs are sufficient to induce severe deficits.[70]

Penicillamine, which chelates metals, will induce depletion of zinc and copper with chronic administration, and may cause loss of taste because of zinc deficiency or possibly copper deficiency.[26, 41]

Alcohol induces excessive losses of potassium, magnesium, and zinc. Excessive alcohol intake may have an added effect with therapeutic drugs in inducing clinical deficiencies of these minerals.[113]

A phosphate depletion syndrome is known to occur in patients on heavy doses of antacids. Antacids producing phosphate depletion are those containing aluminum and/or magnesium hydroxide. Dietary phosphate combines with these antacids to form insoluble aluminum and magnesium phosphates which are excreted by the gastrointestinal tract. The risk of acute phosphate depletion is greatest when there is an interactive effect with a low phosphate diet. Symptoms of phosphate depletion are profound muscle weakness which may be limited to proximal limb muscles, malaise, paresthesia, anorexia, and convulsions. In some patients, phosphate depletion leads to osteomalacia or hemolytic anemia.[94, 113]

Iron deficiency may be induced by chronic intake of aspirin and/or other salicylates or other non-narcotic analgesics such as indomethacin. These drugs cause erosions in the stomach and intestine which are associated with blood loss. Chronic blood loss into the gastrointestinal tract causes iron deficiency anemia.[14, 58]

DRUGS AND VITAMINS

Effects of Drug-Vitamin Interactions on Drug Efficacy

Pharmacologic doses of vitamins can lower blood levels of drugs when these vitamins undergo drug interaction. In these circumstances, the desired therapeutic effects of the primary drug may not be obtained. High doses of folic acid or vitamin B_6 given to patients receiving diphenylhydantoin and/or phenobarbital for seizure disorders may reduce blood levels of these drugs and thereby reduce their therapeutic efficacy.[7, 43, 68]

Hypotheses have been put forward to explain these nutrient-drug interactions. Whereas it has been suggested that both folic acid and pyridoxal phosphate could alter the rate of metabolism of diphenylhy-

dantoin and/or phenobarbital, there are no experimental data to support such a hypothesis. Another possibility as yet untested is that high intakes of folic acid or pyridoxine could inhibit absorption of anticonvulsants.

Vitamin Antagonists

Vitamin antagonists with well-established therapeutic efficacy include coumarin anticoagulants, cancer chemotherapeutic drugs such as methotrexate, and the antimalarial drug, pyrimethamine.

Vitamin K is required for carboxylation of glutamic acid residues in precursor proteins of clotting factors. The storage form of vitamin K in the liver is vitamin K 2,3-epoxide. Matshiner et al.[67] showed that when coumarin or indandione anticoagulants are administered, vitamin K 2,3-epoxide accumulates in the liver. This finding led to a working hypothesis for the mode of action of these anticoagulants. It has been proposed that they function by inhibiting regeneration of vitamin K from the epoxide.[67, 111]

Ren et al.[95] tested this hypothesis in rats by studying effects of nine coumarin and indandione anticoagulants on prothrombin synthesis and on the conversion of vitamin K_1 epoxide to vitamin K. A high degree of correlation was obtained between inhibition of prothrombin synthesis and the level of vitamin K_1 epoxide in the rat liver. Similar effects were observed both in vivo and in vitro.

Biochemical effects of methotrexate include multiple antagonistic actions on folacin metabolism. The drug in the tissues binds firmly to the dihydrofolate reductase enzyme and the enzyme that is bound to the drug decays more slowly than the free enzyme. Utilizable folacin is displaced from the dihydrofolate reductase enzyme and excreted in the urine. Methotrexate polyglutamates are formed, and there is a reduction in the synthesis of polyglutamates derived from folacin. Thymidylate synthetase is inhibited. DNA, RNA, and protein synthesis are inhibited. Cytotoxic effects are selective according to the rate of cell reproduction and self-limiting methotrexate is more effective when cell populations are in the log phase of growth.

The potential of methotrexate as an antitumor agent has been greatly increased since citrovorum factor rescue was introduced into treatment protocols. Citrovorum factor (folinic acid, 5-formyl tetrahydrofolate) can be utilized in the presence of methotrexate-inhibited reductase enzyme, thus reducing methotrexate toxicity with some retention of anti-tumor activity.[29, 46, 121] Enhanced bioavailability of methotrexate may result from dietary manipulation which alters intestinal microflora because intestinal methotrexate metabolism is decreased. However, the use of poorly absorbable antibiotics such as neomycin decreases the bioavailability of this drug.[112] Reversal of antifolate effects of pyrimethamine can be accomplished with folic acid. Citrovorum factor may, however, be required as "rescue" in high dosage pyrimethamine therapy. Binding of pyrimethamine to the dihydrofolate reductase enzyme is less than methotrexate which accounts for the therapeutic efficiency of folic acid supplements.

Antivitamin properties of other drugs are recognized as an avoidable side effect. Isoniazid, cycloserine, levodopa, and penicillamine inhibit the normal metabolism of vitamin B_6 by formation of both drug-vitamin complexes and by inhibition of the pyridoxal kinase enzyme (Table 7).[100]

Vitamins as Rational Therapeutic Agents for Drug Intoxication

RIBOFLAVIN AND BORIC ACID POISONING. A new use for riboflavin may be in the treatment of boric acid poisoning. Boric acid combines with the ribityl side chain of riboflavin and induces massive riboflavinuria. It has further been suggested that in boric acid poisoning, formation of flavin coenzymes may be depressed or the binding of flavin coenzymes to their respective apoenzymes may be impaired. Animal studies indicate that riboflavin has a protective effect against boric acid toxicity.[91, 102]

VITAMIN E AND THE PREVENTION OF BRONCHOPULMONARY DYSPLASIA IN INFANTS. In rats vitamin E has been shown to combat pulmonary oxygen toxicity, while rats deficient in vitamin E are vulnerable for oxygen damage to the lungs.[2, 17, 92]

Chronic lung disease in premature infants treated by mechanical ventilation and with increased concentrations of oxygen in inspired air have developed a severe respiratory distress syndrome designated bronchopulmonary dysplasia. Disease is believed to result from the toxic effects of excess oxygen. In a study by Ehrenkranz,[32] infants at risk for the development of bronchopulmonary dysplasia were protected by administration of vitamin E during the acute phase of the respiratory distress syndrome that required oxygen administration.

Hypovitaminoses and Other Nutritional Changes in Oral Contraceptive Users

Biochemical evidence of vitamin depletion or deficiencies has been obtained among women on oral contraceptives. Whereas subclinical deficiencies of folacin, roboflavin, vitamin B_6, vitamin B_{12}, and vitamin C may be found by laboratory tests, physical signs of these deficiencies can seldom be linked to the oral contraceptive. Whereas depression occuring in women on these drugs has been attributed to vitamin B_6 de-

Table 7. *Vitamin Antagonists*

Folacin antagonists	Methotrexate Pyrimethamine Triamterene Trimethoprim
Vitamin B_6 antagonists	Isoniazid Hydralazine Cycloserine Levodopa
Vitamin K antagonists	Coumarin anticoagulants

ficiency, the association cannot be generalized. It is assumed that if depression is due to vitamin B_6 deficiency, it would be reversed by administration of pyridoxine.[1]

We have shown that in women taking the pill, and in non-users, red cell folacin values are highly correlated with intake of dietary folacin. The risk of serious folacin depletion with megaloblastic anemia developing in pill users is related to inadequate dietary intake of this vitamin, to alcohol abuse, to malabsorption syndromes, and to use of other drugs such as anticonvulsants which elevate folacin requirements.[101]

In a study of the nutritional status of women attending family planning clinics which serve a low income population, we found plasma folacin was correlated positively with age and education and negatively with weight for height for age and triceps skinfold thickness. Findings suggested that in the sample population plasma folacin was an indicator, as was obesity, of poor dietary habits which may be influenced by youth and lack of education. Plasma folacin levels were not affected by intake of the pill; however, women on the pill in these clinics had lower red cell folacin levels than non-users. Both plasma and red cell folacin values increased when physiological vitamin supplements containing folic acid were given.

In this study, women on the pill also tended to show reduced riboflavin status as indicated by red cell glutathione reductase assay.[98]

Newman et al.[82] showed that riboflavin deficiency is common in women of low socioeconomic status in the reproductive period of life. Use of the pill increases the incidence of riboflavin deficiency.

In a 1978 review of the risks and benefits of the pill,[120] a decreased incidence of iron deficiency anemia is cited as a noncontraceptive benefit. Reduced menstrual blood flow in pill users reduces physiological iron losses and improves iron status. Serum iron may be increased but total iron binding capacity is more uniformly elevated.

Changes in composition of contraceptive steroids with reduction in estrogen content suggests a need for re-evaluation of any adverse nutritional effects. It is perhaps significant that in the last two years the numbers of publications on nutrition and the pill has declined.

CONCLUSIONS

Drugs may be discontinued prematurely for many reasons. The drug may have been ineffective or nutrients may have caused an adverse effect on drug bioavailability. Adverse drug reactions may be due to drug-nutrient, drug-food, or drug-alcohol incompatibility, or to drug-induced nutritional deficiencies. A lack of drug efficacy or unwanted drug effects of nutritional etiology related to food or nutrient interaction are predictable and preventable provided that the risk is understood and the patient's diet as well as drug regimen is known to members of the health care team including the physician, nurse, and pharmacist.

REFERENCES

1. Adams, P. W., Rose, D. P., Folkar, D. J., et al.: Effect of pyridoxine hydrochlorode (vitamin B_6) upon depression associated with oral contraception. Lancet, *1*:897, 1973.
2. Aler, D. W.: Effects of vitamin E deficiency on oxygen toxicity in the rat. J. Physiol., *121*:47P-48P, 1953.
3. Arenillas, L.: Amitriptyline and body weight. Lancet, *1*:432-433, 1964.
4. Asatoor, A. M., Levi, A. J., and Milne, M.D.: Tranylcypromine and cheese. Lancet, 2:733-734, 1963.
5. Banks, T. and Nayab, A. 1974 Letter: Digitalis cachexia. New Eng. J. Med. 290:746.
6. Bates, T. R., Sequiera, J. A., and Tembo, A. V.: Effect of food on nitrofurantoin absorption. Clin. Pharmacol. Therap., *16*:63-68, 1974.
7. Bayless, E. M., Crowley, J. M., Preece, J. M., et at.: Influence of folic acid on blood phenytoin levels. Lancet, *1*:62-64, 1971.
8. Bergen, S. S.: Appetite-stimulating properties of cyproheptadine. Amer. J. Dis. Child., *108*:270-273, 1974.
9. Berlin, H., and Bante, G.: Studies on oral utilization of penicillin V. Antibiotics Annual, Med. Encycl. Inc., 1959, pp. 149-157.
10. Blackwell, B., and Mabbit, L. A.: Tyramine in cheese related to hypertensive crisis after monamine oxidase inhibition. Lancet, *1*:938-940, 1965.
11. Blackwell, B., Marley, E., and Mabbit, L. A.: Effects of yeast extract after monamine exidase inhibition. Lancet, *1*:940-943, 1965.
12. Blomley, B. J.: Monamine oxidase inhibitors. Lancet, 2:1181-1182, 1964.
13. Blundell, J. E., Latham, C. J., and Leshem, M. B. Differences between the anorexic actions of amphetamine and fenfluramine — possible effects on hunger and satiety. J. Pharm. Pharmac., *28*:471-477. 1976.
14. Boardman, P. L., and Hart, E. D.: Side effects of indomethacin. Ann. Rheum. Dis., *26*:127-132, 1967.
15. Buck, R. W.: Mushroom toxins — brief review of the literature. New Eng. J. Med., *265*:681-686, 1961.
16. Chesney, R. W., Hamstra, A. J., Mazees, R. B., et al.: Reduction of serum-1,25-dihydroxy vitamin-D in children receiving glucocorticoids. Lancet, 2:1123-1125, 1978.
17. Clark, J. M., and Lambertson, C.J.: Pulmonary oxygen toxicity: A review. Pharmacol. Rev., *23*:38-133, 1971.
18. Corto, T. A., Fleming, C. R., and Malageldad, J-R.: Improved nutrient absorption after cimetidine in short-bowel syndrome with gastric hypersecretion. New Eng. J. Med., *300*:79-80, 1978.
19. Craft, A. W., Kay, A. G. M., Lawson, V. N., et al.: Methotrexate induced malabsorption in children with acute lymphoblastic leukemia. Brit. Med. J., 2:1511-1512, 1977.
20. Crane, G. E.: Clinical psychopharmacology in its 20th year. Science, *181*:124-128, 1973.

20a. Crisp, A. H.: A treatment regime for anorexia nervosa, Brit. J. Psychiatry, *112*:505–512, 1965.

21. Cronk, G. A., Naumann, D. E., Albright, H., et al.: Laboratory and clinical studies with potassium penicillin-152 (potassium (α-phenoxyethyl)-penicillin). Antibiotics Annual, 1959-1960. Med. Encycl. Inc., 1960, pp. 133-145.
22. Cronk, G. A., Wheatley, W. B., Fellers, G. F., et al.: The relationship of food intake to the absorption of potassium alpha-phenoxyethyl penicillin and potassium phenoxymethyl penicillin from the gastrointestinal tract. Amer. J. Med. Sci., 240:219-225, 1960.
23. Crounse, R. G.: Humán pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. J. Invest. Dermat., *37*:529-533, 1961.
24. Crisp, A. H.: Anorexia nervosa — "feeding disorder," "nervous malnutrition" or "weight phobia?" World Rev. Nutr. Dietet., *12*:452-504, 1970.
25. Datey, K. K., Kelar, P. N., and Pandya, R. S.: Fenfluramine in the management of obesity. Brit. J. Clin. Pract., 27(10):373-375, 1973.
26. Day, A. T., Golding, J. R., Lee, P. N., et al.: Penicillamine in rheumatoid disease: A long-term study. Brit. Med. J., *1*:180, 1974.
27. DeWyss, W. D.: Abnormalities of taste as a remote effect of a neoplasm. Ann. N.Y. Acad. Sci., *230*:427, 1974.
28. Diamond, M. A., Murray, R. H., and Schmid, P.: Treatment of idiopathic postural hypertension with oral tyramine (Ty) and monamine oxidase inhibitor (MI). J. Clin. Res., *17*:237, 1969.
29. Djerassi, I.: High-dose methotrexate (NSC-740) and citrovorum factor (NSC-3590)

rescue: Background and rationale. Cancer Chemotherap. Rep., Part III, 6:3-6, 1975.
30. Drash, A., Elliott, J., Langs, H., et al.: Effect of cyproheptadine on carbohydrate metabolism. Clin Pharm. Therap., 7:340-346.
31. Duarte, G. C., Winnacker, J. L., Becker, K. L., et al.: Thiazide-induced hypercalcemia. New Eng. J. Med., 284:828-830, 1971.
32. Ehrenkranz, R. A., Bonta, B. W., Ablor, R. C., et al.: Amelioration of bronchopulmonary dysplasia after vitamin E administration. A preliminary report. New Eng. J. Med., 299:564-569, 1978.
33. Evans, E., and Miller, D. S.: Bulking agents in the treatment of obesity. Nutr. Metab., *18*:199-203, 1975.
34. Finkelstein, W., and Isselbacher, K. J.: Drug therapy: Cimetidine. New Eng. J. Med., 299:992-996, 1978.
35. Fitzgerald, M. G., et al.: Alcohol sensitivity in diabetics receiving chlorpropamide. Diabetes, 2:40, 1962.
36. Fleming, B J., Genuth, S. M., Gould, A. B., et al.: Laxative-induced hypokalemia, sodium depletion and hyperreninemia. Effects of potassium and sodium replacement on the renin-angiotensinaldosterone system. Ann. Intern. Med., 83:60-62, 1975.
37a. Gander, D. R., and Lond, M. B.: Treatment of depressive illnesses with combined antidepressants. Lancet, 2:107-109, 1965.
37. Gibaldi, M., and Grundhofer, B.: Biopharmaceutic influences on the anticholinergic effects of propantheline. Clin. Pharmacol. Ther., *18*:457-461, 1975.
38. Gill, G. V.: Rifampicin and breakfast. Lancet, 2:1135, 1976.
39. Gillespie, N. G., Mena, I., Cotzias, G. C., et al.: Diets affecting parkinsonism with levodopa. J. Amer. Diet. Assoc., 62:525-528, 1973.
40. Gnader, D. R.: Treatment of depressive illnesses with combined antidepressants. Lancet 2:107, 1965.
41. Gordon, M. H., and Ahrlich, G. E.: Penicillamine for treatment of rheumatoid arthritis. J.A.M.A., 229:1342-1343, 1974.
42. Griffin, J. P., and D'Arcy, P. F.: A Manual of Adverse Drug Reactions. John Wright & Sons, Ltd., Bristol, England, 1975, pp. 60-61.
43. Hansson, O., and Sillanpan, A. M.: Doxine and serum concentrations of phenytoin and phenobarbitone. Lancet, *1*:256, 1976.
44. Hansten, P. D.: Drug Interactions. Philadelphia, Lea and Febiger, 2nd ed., 1973, p. 214.
45. Hodge, J. V., Nye, E. R., and Emerson, G. W.: Monamine oxidase inhibitors, broad beans and hypertension. Lancet, *1*:1108, 1964.
46. Hoffbrand, A. V.: Synthesis and breakdown of natural folates (folate polyglutamates). *In* Progress in Hematology, IX. New York, Grune & Stratton, 1975, pp. 85-105.
47. Horwitz, D., Lowenberg, W., Engelman, K., et al.: Monamine oxidase inhibitors, tyramine and cheese. J. Am. Med. Assoc., *188*:1108-1110, 1964.
48. Houston, J. B., and Levy, G.: Effect of carbonated beverages and an antiemetic containing carbohydrate and phosphoric acid on riboflavin bioavailability and salicylamide biotransformation in humans. J. Pharm. Sci., 64:1504-1507, 1975.
49. Hunt, J. N.: Gastric emptying in relation to drug absorption. Amer. J. Digest Dis., *8*:885-894, 1963.
50. Jaffee, J. J., Colaizzi, J. L., and Barry, H.: Effects of dietary components on GI absorption of acetaminophen tablets in man. J. Pharm. Sci., 60:1646-1650, 1971.
51. Johnson, D. N.: Effect of diazepam on food consumption in rats. Psychopharmacology, 56:111-112.
52. Jusko, W. J. and Levy, G.: Absorption, metabolism and excretion of riboflavin-5′-phosphate in man. J. Pharm, Sci., 56:58-62, 1967.
53. Kappas, A., Anderson, K. E., Conney, A. H., et al.: Influence of dietary protein and carbohydrates on antipyrine and theophylline metabolism in man. Clin. Pharmacol. Therap., 30:643-653, 1976.
54. Kappas, A., Alvares, A. P., Anderson, K. E., et al.: Effect of charcoal-broiled beef on antipyrine and theophylline matabolism. Clin. Pharm. Therap., 23:445-450, 1978.
55. Kelly, M. R., Cutler, R. E., Forrey, A W., et al.: Pharmacokinetics of orally administered furosemide. Clin. Pharmacol. Ther., *15*:178-186, 1974.
56. Kent Smith, C., and Durack, D. T.: Isoniazid and reaction to cheese. Ann. Intern. Med., *88*:520-521, 1978.
57. Koch-Weser, J.: Bioavailability of drug. New Eng. J. Med., 291:233-237, 1974.
58. Leonards, J. R., and Levy, G.: Gastrointestinal blood loss during prolonged aspirin administration. New Eng. J. Med., 289:1020-1022, 1973.
59. Levy, G., and Jusko, W. J.: Factors affecting the absorption of riboflavin in man. J. Pharm. Sci., 55:285-289, 1966.

60. Levy, R. H., Pitlick, W. H., Troupin, A. S., et al.: Pharmacokinetics of carbamazepine in normal man. Clin Pharmacol. Therap., *17*:657-668, 1975.
61. McCarthy, C. G., and Finland, M.: Absorption and excretion of four penicillins; penicillin G, penicillin V, penethicillin and Phenymercaptomethyl penicillin. New Eng. J. Med., *263*:315-326, 1960.
62. MacDonald, H., Place, V. A., Falk, H., et al.: Effect of food on absorption of sulfonamides in man. Chemotherapia, *12*:282-285, 1967.
63. MacFarlane, M.D.: Penicillamine and zinc. Lancet, *2a*:962, 1974.
64. Mainguet, P.: Effect of cyproheptadine on anorexia and loss of weight in adults. Practitioner, *208*:797-800, 1972.
65. Mao, C. C., and Jacobson, E. D. Intestinal absorption and blood flow. Amer. J. Clin. Nutr., *23*:820-823, 1970.
66. Marley, E., and Blackwell, B.: Interactions of monamine oxidase inhibitors, amines and foodstuffs. Adv. Pharmacol. Chemotherap., *8*:185-239, 1970.
67. Matschiner, J. T., Bell, R. G., Amelotti, J. M., et al.: Isolation and characterization of new metabolite of phylloquinone in the rat. Biochem. Biophys. Acta, *201*:309-315, 1970.
68. Mattson, R. A., Gallagher, B. B., Reynolds, G. H., et al.: Folate therapy in epilepsy. A controlled study. Arch. Neurolog. (Chicago), *29*:78-81, 1971.
69. Melander, A.: Influence of food on the bioavailability of drugs. Clin. Pharmacokinet., *3*:337-351, 1978.
70. Melander, A., Danielson, K., Hanson, A., et al.: Enhancement of hydralazine bioavailability by food. Clin. Pharmacol. Therap., *22*:104-107, 1977.
71. Melander, A., Danielson, K., Schersten, B., et al.: Enhancement by food of canrenone bioavailability from spironolactone. Clin. Pharmacol. Therap., *22*:100-103, 1977.
72. Melander, A., Danielson, K., Schersten, B., et al.: Enhancement of the bioavailability of propranolol and metoprolol by food. Clin. Pharmacol. Therap., *22*:108-112, 1977.
73. Miller, D. S., Sterling, J. L., and Yudkin, J.: Effect of ingestion of milk on concentrations of blood alcohol. Nature, *212*:1051, 1966.
74. Modell, W.: Status and prospect of drugs for overeating. J.A.M.A., *173*(10):1131-1136, 1960.
75. Morrison, S. D.: Origins of anorexia in neoplastic disease. Amer. J. Clin. Nutr., *31*:1104-1107, 1978.
76. Murdoch Ritchie, J.: The aliphatic alcohols. *In* Goodman, L. S. and Gilman, A., eds.: The Pharmacological Basis of Therapeutics. Macmillan Co., New York, 3rd ed., pp. 155-156.
77. Murphy, J. P., Jr., King, D. R., and Dubois, A.: Treatment of gastric hypersecretion with cimetidine in the short-bowel syndrome. New Eng. J. Med., *300*:80-81, 1978.
78. Nardone, D. A., McDonald, W. J., and Girard, D. E.: Mechanisms in hypokalemia: Clinical correlations. Medicine, *57*:435-446, 1978.
79. Neuvonen, P. J., Gothini, G., Hackman, R., et al.: Interference of iron with the absorption of tetracyclines in man. Brit. Med. J., *4*:532-534, 1970.
80. Neuvonen, P., Matilla., M., Gothini, G., et al.: Interference of iron and milk with absorption of tetracycline. Scand. J. Clin. Lab. Invest. (Suppl.), *27*:76, 1971.
81. Neuvonen, P. G., and Turakka, H.: Inhibitory effect of various iron salts on the absorption of tetracycline in man. Eur. J. Clin. Pharmacol., *7*:357-360, 1974.
82. Newman, L. J., Lopez, R., Cole, A. S., et al.: Riboflavin deficiency in women taking oral contraceptive agents. Amer. J. Clin. Nutr., *31*:247-249, 1978.
83. Nuessle, W. F., and Norman, F. C.: Pickled herring and tranylcypromine reaction. J.A.M.A., *192*:726-727, 1965.
84. O'Keefe, S. J. D., and Marx, V.: Lunch-time gin and tonic: A cause of reactive hypoglycaemia. Lancet, *1*:1286-1287, 1977.
85. Pantuck, E. J., Hsiao, K. C., Loub, W. D., et al.: Stimulatory effect of vegetables on intestinal drug metabolism in the rat. J. Pharmacol. Exper. Therap., *198*:278-283, 1976.
86. Pawan, G. L. S.: Drugs and appetite. Proc. Nutr. Soc., *33*:239-244.
87. Paykel, P. S., Mueller, P. S., and De La Vergne, P. M.: Amitriptyline, weight gain and carbohydrate craving; a side effect. Brit. J. Psychiat., *123*:501-507, 1973.
88. Penick, S. B., et al.: Metronidazole in the treatment of alcoholism. Amer. J. Psychiat., *125*:1063, 1969.
89. Petrie, J. C., Durno, D., and Howie, J. G. R.: Drug interaction in general practice. *In* Cluff, L. E., and Petrie, J. C., eds.: Clinical Effects of Interaction Between Drugs. Amsterdam, Exerpta Medica., 1974, pp. 237-253.
90. Pettinger, W. A., and Oates, J. A.: Supersensitivity to tyramine during monamine oxidase inhibition in man. Mechanism at the level of the adrenergic neuron. Clin. Pharmacol. Therap., *9*:341, 1968.

91. Pinto, J., Huang, W. P., McConnell, R. J., et al.: Increased urinary riboflavin excretion resulting from boric acid ingestion. J. Lab. Clin. Med., 22:126-134, 1978.
92. Polin, R. L., Bolliner, R. O., Bozynski, M. E., et al.: Effect of vitamin E deficiency on pulmonary oxygen toxicity. Pediatr. Res., *11*:577, 1977.
93. Pyke, D. A., and Leslie, R. D. G.: Chlorpropamide-alcohol flushing: A definition of its relation to non-insulin-dependent diabetes. Brit. Med. J., 2:1521-1522, 1978.
94. Ravid, M., and Robson, M.: Proximal myopathy caused by iatrogenic phosphate depletion. J.A.M.A., 236:1380-1381, 1976.
95. Ren, P., Stark, P. Y., Johnson, R. L., and Bell, R. G.: Mechanism of action of anticoagulants: Correlation between the inhibition of prothrombin synthesis and the regeneration of vitamin K_1 from vitamin K_1 hypoxide. J. Pharmacol. Exper. Therap., *201*:541-546, 1977.
96. Reynolds, W. A., and Lowe, S. H.: Mushrooms and a toxic reaction to alcohol. Report of 4 cases. New Eng. J. Med., 272:630-631, 1965.
97. Roe, D. A.: Alcohol and the Diet. Westport, Connecticut, AVI Publ. Co., in press.
98. Roe, D. A.: Assessment of Need for Nutritional Counselling as a Component of Family Planning Information and Education Services. Final Report, HSA 240-BCHS-106(6)DE, Washington, D.C., 1977.
99. Roe, D. A.: Diet-drug interactions and incompatibilities. *In* Hathcock, J. N., and Coon, J., ed.: Nutrient and Drug Interactions. New York, Academic Press, 1978, pp. 319-345.
100. Roe, D. A.: Drug-Induced Vitamin Deficiencies. Westport, Connecticut, AVI Publ. Co., 1976.
101. Roe, D. A.: Nutrition and the contraceptive pill. *In* Winick, M., ed.: Nutritional Disorders of American Women. New York, John Wiley and Sons, pp. 37-49, 1977.
102. Roe, D. A., McCormick, D. B., and Linn. R-T.: Effects of riboflavin on boric acid toxicity. J. Pharm. Sci., *61*:1082, 1972.
103. Roe, D. A., Wrick, K., McLain, D., et al.: Effects of dietary fiber sources on riboflavin absorption. Fed. Proc., *37*:756, 1978 (Abstract).
104. Safer, D. J., and Allen R. O.: Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. Pediatrics, 5:660-667, 1973.
105. Safer, D., Allen, R., and Barr, E.: Depression of growth in hyperactive children on stimulant drugs. New Eng. J. Med., 287:7-20, 1972.
106. Safer, D. J., Allen, R. P., and Barr, E.: Growth rebound after termination of stimulant drugs. Pediat. Pharm. Therap., *86*:113-116, 1975.
107. Schelme, R. R.: Metabolism of foreign compounds by gastrointestinal microorganisms. Pharmacol. Rev., 25:451-523, 1973.
108. Schreiner, J., and Altemeier, W. A.: Experimental study of factors inhibiting absorption and effective therapeutic levels of declomycin. Surg. Gynec. Obstet., *114*:9-14, 1962.
109. Sedman. A. J., Wilkinson, P. K., Sakmar, E., et al.: Food effects on absorption and metabolism of alcohol. Quart. J. Stud. Alc., *37*:1197-1214, 1976.
110. Seixas, F. A.: Alcohol and its drug interactions. Ann. Intern. Med., *83*:86-92, 1975.
111. Shearer, M. J., McBurney, A., Breckinridge, A., et al.: Dose-response relationships between warfarin and the metabolism of phylloquinone (vitamin K_1) in man. Int. J. Vitam. Nutr. Res., *46*:215-219, 1976.
112. Shen, D. D., and Azarnoff, D. L.: Clinical pharmacokinetics of methotrexate. Clin. Pharmacol. Kinet., 3:1-13, 1978.
113. Shields, H. M.: Rapid fall of serum phosphorus secondary to antacid therapy. Gastroenterology, 75:1137-1141, 1978.
114. Shneerson, J. M., and Gazzard, D. G.: Reversible malabsorption caused by methyldopa. Brit. Med. J., 2:1456-1457, 1977.
115. Spiers, A. S. D., and Malone, H. R.: Effect of food on aspirin absorption. Lancet, *1*:440, 1967.
116. Spivack, S. D.: Procarbazine. Ann. Intern. Med., *81*:795-800, 1974.
117. Stiel, J. N., Liddle, G. W., and Lacy, W. W.: Studies on mechanism of cyproheptadine-induced weight gain in human subjects. Metabolism, *19*:192-200, 1970.
118. Suki, W., Yium. J. J., VonMinden, M., et al.: Acute treatment of hypercalcemia with furosemide. New Eng. J. Med., *283*:836-840, 1970.
119. Van Praag, H. M.: Abuse of, dependence on and psychoses from anorexigenic drugs. *In* Meyler, L., ed.: Drug-Induced Diseases. New York, North Holland Publ. Co., 1968, pp. 281-294.
120. Vessey, M. P.: Contraceptive methods: risks and benefits. Brit. Med. J., 2:721-722, 1978.
121. Wan, S. H., Hoffman, D. H., Azarnoff, D. L., et al.: Effect of route of administration and infusions on methotrexate pharmacokinetics. Cancer Res., *34*:3487-3491, 1974.

122. Welling. P. G.: Influence of food and diet on gastrointestinal absorption: A review. J. Pharmacokinet. Biopharm., 5:291-334, 1977.
123. Welling, P. G., Huang, H., Koch, P. A., et al.: Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects. J. Pharm. Sci., 66:549-552, 1977.
124. Welling, P. G., Lyons, L. L., Tse, F. L. S., et al.: Propoxyphene and norpropoxyphene: Influence of diet and fluid on plasma levels. Clin. Pharmacol. Therap., 19:559-565, 1975.
125. Zintel, H. A.: Nutrition in the care of the surgical patient. *In* Wohl, M. G., and Goodhart, R. S., eds.: Modern Nutrition in Health and Disease. Philadelphia, Lea and Febiger, 1968.

Division of Nutritional Sciences
Cornell University
Ithaca, New York 14853

Nutritional Problems Induced by Cancer

*Maurice E. Shils, M.D., Sc.D.**

NUTRITIONAL EFFECTS INDUCED BY CANCER

Systemic Effects

Anorexia

A striking and presently unexplained effect of active neoplastic disease in a significant number of patients is the marked anorexia and wasting ("cancer cachexia") not directly attributable to obvious intestinal obstruction, sepsis, endocrine disorder, or other anatomic lesions. Although anorexia is not unique to cancer, its high incidence and prolonged and deleterious effect make it of special concern. It is manifested most commonly and noticeably in patients with cancer in one or more areas of the alimentary tract including liver and pancreas[51] and in those with widely disseminated disease. Its cause is uncertain, although it and the weight loss seen in cancer have been the subject of many publications and conferences.[15, 42-44, 61]

The weight loss experienced by many cancer patients is, for the major part, attributable to inadequate food intake resulting from anorexia. It is common for such patients to ingest breakfast fairly well and then to eat progressively less of succeeding meals over the day. Often the anorexia is associated with alterations in taste and patients are prone to ascribe diminished appetite to the unpleasant taste of one or more foods. Efforts have been made to begin to dissect out the prevalence and types of taste alterations in cancer patients.[16, 70] It is the opinion of this author that available data must be viewed as preliminary and variable to the point of being of questionable value. More precise studies are essential before one can establish the patterns (if any) that occur in relation to the type and stage of various malignant processes. Alterations in taste are probably not primary factors in anorexia but are associated with more basic changes initiated by tumors in association with psychosomatic factors.

* Associate Professor of Medicine, Cornell University Medical College; Director of Nutrition and Attending Physician, Memorial Sloan-Kettering Cancer Center, New York, New York

Changes in Energy Metabolism

Various investigators have suggested that cancer *per se*, apart from depressed food intake, alters energy metabolism so that requirements are increased beyond those of normal individuals of otherwise similar status. Young[73] has reviewed eight reports published between 1922 and 1974 on the basal metabolic rate of cancer patients. The results were very variable, the cases relatively few and the available information limited; however, the majority indicated a tendency toward elevation especially in patients with leukemia and Hodgkin's disease. In a more recent study, energy intake (mean 1270 kcal/day) though varying greatly in cancer patients, was not significantly different from that of the controls (mean 1470 kcal/day). Both the daily energy expenditure (mean 2020 kcal/24 hours) and the resting metabolic rate (mean 1630 kcal/24 hours) were significantly greater in the cancer patient than in the controls (mean 1420 and 1170 kcal/24 hours, respectively).[71] The variability of energy intake and expenditure of the cancer patient was great and there was a cluster of cancer patients with expenditure similar to that of controls.

While more data are needed, there is reasonable evidence that some cancer patients do have increased resting metabolic expenditure, often occurring in a setting of decreased energy intake. Obviously, the anorexia is working against the nutritional interest of the patient by limiting caloric intake during a period of normal or increased expenditure. In the latter case, the patient is at increased risk of depletion during periods of impaired food intake.

A number of metabolic changes may occur in cancer patients and modify energy expenditure. Fever, surgery, and other causes of stress with increased production of corticosteroids and catecholamines are not uncommon and these increase protein catabolism with increased gluconeogenesis.[71, 73] However, in addition to such known stimulatory effects on energy requirements, consideration must be given to the effects of the malignant lesions, per se, on metabolic changes. It has been proposed that the increased rate of resynthesis of glucose from lactate (Cori cycle) produced by the tumor results in a significant energy drain on host tissues. Cori cycle activity has been measured in a heterogeneous group of patients with metastatic carcinoma and found to be increased in those with progressive weight loss.[30] It has been pointed out, however, that increased Cori cycle activity does not appear to account for a significant fraction of daily energy expenditure.[73] It has been proposed also that cancer patients have increased energy cost as the result of increased conversion of glucose to fat before being metabolized.[67]

Barry has found that malnourished patients with extra alimentary tract malignant diseases often had abnormalities of mucosal histology, epithelial cell loss and lactose utilization; however, he found that similar changes occurred in seriously malnourished patients without cancer and suggested that such mucosal changes are the result of malnutrition rather than the direct cause of cachexia or the direct effects of malignant lesions outside the gastrointestinal tract.[4] Once present,

of course, impaired mucosal function can contribute further to malnutrition by depressed efficiency of absorption. It has also been found that the disappearance rate of intravenous glucose is significantly lower in cachectic cancer patients as compared to non-cachectic cancer patients and tumor-free controls and that the former did not respond normally to glucagon; this suggests an impairment of insulin release with cachexia.[31]

"LOCALIZED" TUMOR EFFECTS

In addition to systemic effects, various neoplasms may have a number of more localized effects leading to nutritional problems. Some of these are listed in Table 1.

By far the most common causes of malnutrition in this general category are interferences with food intake as a result of partial or complete obstruction of some portion of the gastrointestinal tract. Relief of obstruction by surgical or other treatment is necessary. Nutritional support by intravenous alimentation or tube feeding into a site distal to the obstruction may be very useful in sustaining such patients until normal oral feedings can be reinstituted following effective surgical or other therapy.

Table 1. *Some Effects of Neoplastic Diseases on Nutritional Status**

1. Malnutrition secondary to persistent anorexia.
2. Malnutrition associated with impaired food intake secondary to obstruction.
3. Malabsorption associated with:
   a. Deficiency of pancreatic enzymes or bile salts.
   b. Infiltration of small bowel by neoplasms, such as lymphoma or carcinoma.
   c. Fistulous bypass of small bowel.
   d. Gastric hypersecretion inhibiting pancreatic enzymes (in Zollinger-Ellison syndrome).
   e. Blind loop secondary to partial upper small bowel obstruction.
   f. Malnutrition–induced villous hypoplasia.
4. Protein-losing enteropathy (e.g., in gastric carcinoma, lymphoma or with lymphatic obstruction).
5. Electrolyte and fluid balance disturbances associated with:
   a. Persistent vomiting in obstruction.
   b. Vomiting secondary to increased intracranial pressure from tumors.
   c. Small bowel fluid losses from fistula.
   d. Diarrhea associated with hormone-secreting tumors (e.g., carcinoid syndrome, Zollinger-Ellison syndrome, Verner-Morrison syndrome) and villous adenoma of the colon.
   e. Inappropriate antidiuretic hormone secretion associated with certain tumors.
   f. Hyperadrenalism secondary to excessive corticotropin or corticosteroid production by tumors.
   g. Hypercalcemia secondary to ectopic parathyroid hormone-like agents.

*From Shils, M. E.: Nutrition and neoplasia. *In* Goodhart, R., and Shils, M., eds.: Modern Nutrition in Health and Disease. Philadelphia, Lea & Febiger, 6th ed., 1979. Reproduced with permission.

Causes of Malabsorption Syndromes

Involvement of the pancreas, pancreatic duct, or common bile duct may lead to impaired digestion and absorption of fats and fat soluble vitamins. Decreased fat absorption is associated with increased fecal losses of calcium and magnesium.[8] In addition, proteins may be much less efficiently absorbed with serious pancreatic insufficiency. The use of parenteral vitamin K and other fat-soluble vitamins is often helpful in restoring the patient to the best possible nutritional state for surgical procedures in such situations. Pancreatic insufficiency may be associated with impaired vitamin B_{12} absorption.[62]

ASSOCIATION OF CARCINOMA, LYMPHOMA AND INTESTINAL MUSOSAL ABNORMALITIES. Bossak et al.[9] reviewed 94 patients with celiac disease (gluten enteropathy, non-tropical sprue), five of whom had intestinal carcinomas. Harris et al.[27] reported 202 patients with adult celiac disease or sprue, 14 of whom had carcinomas of the alimentary tract, 6 being in the esophagus. Various hypotheses have been suggested for the carcinomatous involvement in these patients including possibilities that the abnormal small bowel epithelium permits increased absorption of carcinogens, that the chronic inflammation of the lamina propria or lymphoid hyperactivity somehow plays a role, or that environmental factors such as prolonged nutritional deficiency secondary to malabsorption or intestinal organisms may account for the malignant changes.

In 1962 Gough et al.[23] advanced the hypothesis that small bowel reticulosis may develop as a complication in patients with celiac syndrome. Austed et al.[3] found a 10 per cent incidence of lymphoma in their celiac patients. Benson et al.[7] reported an incidence of 6.2 per cent, and Harris et al.[27] reported an incidence of 6.9 per cent (with a similar incidence of carcinoma in their series of 202 patients). Many of the older studies had no histologic proof of villous atrophy by biopsy and the diagnosis of celiac syndrome was made by history or abnormal fat absorption and/or in response to gluten free diets.

Lymphoma involving the small bowel mesenteric lymph nodes may present as malabsorption.[22, 45] Because of this relationship lymphoma should be suspected with the onset of the celiac syndrome in middle age especially, but also in young people particularly with certain racial backgrounds.[22] Men over 40 years of age with long-standing celiac syndrome who are not on a gluten-free diet are a major risk group. The mechanisms for the development of malabsorption with intestinal lymphoma are several. The intestinal epithelium may be disrupted by the generalized villous atrophy found in association with lymphomatous involvement. Infiltration of the lamina propria and draining lymph nodes can lead to obstruction of mesenteric lymph channels and dilation of the lymphatics within the intestinal villi which in turn can lead to development of a protein-losing enteropathy with hypoalbuminemia, hypoglobulinemia, and lymphocytopenia[21, 65] Protein-losing enteropathy has also been described with cases of gastric carcinoma.[65]

The blind loop syndrome in the upper small bowel secondary to partial obstruction with bacterial overgrowth may also result in steatorrhea and vitamin B_{12} deficiency. The blind loop syndrome involves not only direct interaction of bacteria with certain nutrients but also the development of abnormalities of the intestinal epithelium to account for associated malabsorption.[32]

Bypass of small bowel as a result of gastrocolic and jejunocolic fistulas may also occur in the course of abdominal cancer, with significant malabsorption and electrolyte and fluid disturbances.

Nutritional replacement and support in such malabsorption syndromes are useful while direct antineoplastic treatment with surgery, radiation, and chemotherapy are undertaken.

Ectopic Hormones

An area of expanding interest concerns the secretion by tumors of a variety of potent pharmacologic substances, including steroids, hormone polypeptides, kinins and prostaglandins.[17] A wide variety of nutritional-metabolic problems may develop in patients with such hormone-secreting neoplasia, some of which may produce more than one active agent. Diarrhea may occur with gastrin-secreting islet cell adenomas (Zollinger-Ellison syndrome),[14] tumors, primarily of the pancreas (but also of the bronchus and ganglioneuroblastoma), which secrete vasoactive inhibitory peptide (VIP) and other hormones (Verner-Morrison syndrome or "pancreatic cholera")[43, 63] malignant carcinoid tumors of the intestine[35] medullary carcinoma of the thyroid,[60, 69] villous adenoma,[12] and ganglioneuroma.[50] Losses of potassium and fluid with Verner-Morrison syndrome and villous adenoma may be severe. Steatorrhea occurs in the Zollinger-Ellison syndrome; this has been attributed partly to inactivation of pancreatic lipase by excessive acid production in the stomach and partly to villous damage.[57] While the diarrhea of carcinoid is usually of the watery type, cases of steatorrhea have been reported.[35]

Hyponatremia, fluid retention, and increased urinary sodium losses attributable to inappropriate secretion of antidiuretic hormone have been described, most commonly in association with, but not restricted to, bronchogenic and oat cell carcinoma.[33] Medullary carcinoma of the thyroid gland (generally part of multiple endocrine adenomatosis, type III) secretes excessive amounts of calcitonin[60] as well as prostagladins[69] and histamine,[5] and may be associated with pheochromocytoma.[51] Calcitonin induces secretion of water and electrolytes by the jejunal mucosa, thereby explaining the diarrhea.[25]

There are reports of malabsorption and diarrhea occurring in patients with systemic mastocytosis, a disease associated with increased secretion of histamine from the mast cells.[2] Electrolyte disturbances and increased nitrogen and calcium losses often occur in the hyperadrenal state, induced either by the secretion of adrenal cortical carcinoma, or less frequently, by corticotropin secreted by certain solid tumors, especially those in the lung.[38]

Other Fluid and Electrolyte Disturbances

The major causes of fluid and electrolyte disturbances in cancer patients are vomiting and diarrhea, secondary to partial or complete obstruction, and gastric and small bowel fluid losses through a fistula. Losses of sodium, chloride, potassium, magnesium, and zinc may be serious with large intestinal losses.

Fluid and electrolyte imbalances are often seen in patients with widespread hepatic metastases, ascites and liver failure, with cardiac metastases and failure, with metastatic ovarian carcinoma and ascites, with renal failure secondary to obstruction of the urinary tract by tumor, with obstruction of lymphatic or venous drainage in major areas and other situations listed in Table 1 and described above.

Hypoalbuminemia and Anemia

Hypoalbuminemia and anemia are also frequently noted with advanced cancer. The depressed albumin levels are usually secondary to (1) inability to produce sufficient albumin (as a result of serious protein-calorie deficiency, the metabolic effects of certain tumors or hepatic insufficiency secondary to parenchymal cell damage or replacement by tumor), (2) losses of albumin from the body in excess of synthetic capacity, e.g., protein-losing enteropathy or nephrotic syndrome, (3) dilution of albumin into abnormally large extracellular compartments (e.g., ascites and edema), or a combination of these. Hypoalbuminemia will respond to appropriate nutritional therapy when malnutrition is the primary or an important contributory factor. Anti-tumor therapy is obviously indicated to treat the direct effects of neoplastic growth. The anemia may be secondary to insufficiency of hematopoietic nutritional factors and the cause of the anemia must be evaluated. A normochromic normocytic anemia is frequently associated with cancer and does not respond to nutritional factors. Radiation and chemotherapy may also be contributing factors.

Vitamins

Vitamin levels may be low in cancer patients. Undoubtedly, much of the depletion is secondary to poor intake, exacerbated in some by losses through abnormal alimentary tract and renal function.

Abnormalities in folate metabolism may occur in acute and chronic leukemias.[58] Patients with leukemias, disseminated lymphomas,[49] and various metastatic carcinomas[40] tend to have low serum folate levels. It has been known for some time that serum vitamin B_{12} levels are elevated in certain leukemias[26] and in the presence of metastatic liver disease.[4]

Trace Elements

Increasing attention is being given to the trace element status of cancer patients as the result of our improving understanding of their importance. The available data are primarily those of the survey type of serum and urine levels and some tissue concentrations with little knowledge of associated or etiologic factors. As with water-soluble vita-

mins and other minerals, trace element levels will reflect the intake, basic needs, and losses. Impaired intake and/or increased excretion secondary to organ disease will lower serum values. Zinc losses are significant in small bowel drainage and this is reflected in low serum levels.[34] Failure to provide this and other essential trace elements in intravenous or tube feedings will exacerbate the problem. Since copper and manganese are dependent on bile secretion as a major avenue of elimination, increased levels of these elements occur with intrahepatic and extrahepatic biliary obstruction. Rapid tissue breakdown with chemotherapy or radiation will increase excretion, and, in association with renal dysfunction, lead to rises in serum levels of those trace elements ordinarily excreted into the urine. The literature on serum, urine, and tumor tissue trace element levels in various types of malignant diseases has been reviewed.[52]

Treatment of Metabolic and Nutritional Changes

Reversal for any significant period of the undesirable metabolic and nutritional changes secondary to systemic and localized effects of cancer depends primarily upon elimination of the malignant lesion entirely or in large part. The physician frequently faces the problem of having to correct significant malnutrition and fluid and electrolyte imbalances in patients requiring surgical procedure or in those who need to be maintained in the best possible state for as long as possible in order to permit a therapeutic trial of radiation or chemotherapy. For such patients, careful attention and a positive approach to correction of abnormalities are indicated. As with all chronic wasting diseases, one cannot and should not expect to restore significant amounts of tissue in a short period of time. Urgent surgical intervention cannot wait upon achievement of the goal of nutritional rehabilitation. In such a situation correction of acute or chronic vitamin and mineral deficiencies, blood loss, and electrolyte and fluid imbalances can often be accomplished within a matter of days and this achievement improves the surgical risk. When surgery is indicated for a debilitated patient and when there have been and are likely to be prolonged periods of little or no oral intake of food, an attempt to restore improved nutritional and metabolic status by addequate parenteral administration or tube feeding may be an aid to survival or to decreased morbidity and the period of convalescence.

NUTRITIONAL PROBLEMS ARISING FROM THE TREATMENT OF CANCER

Significant nutritional problems may arise as the result of the specific treatment given to control the neoplastic disease (Table 2).

Radiation Therapy

Radiation of the head and neck may have serious psychological, physiological, and nutritional aftereffects.[19] The resulting loss of taste

Table 2. *Consequences of Cancer Treatment Predisposing to Nutritional Problems**

1. Radiation treatment
   a. Radiation of oropharyngeal area
      (1) Destruction of sense of taste; xerostomia and odynophagia; loss of teeth
   b. Radiation to lower neck and mediastinum
      (1) Esophagitis with dysphagia
      (2) Fibrosis with esophageal stricture
   c. Radiation of abdomen and pelvis
      (1) Bowel damage, acute and chronic, with diarrhea, malabsorption, stenosis and obstruction, fistulization

2. Surgical treatment
   a. Radical resection of oropharyngeal area
      (1) Chewing and swallowing difficulties
      (2) Tube feeding may be required
   b. Esophagectomy and esophageal reconstruction
      (1) Gastric stasis and hypochlorhydria secondary to vagotomy
      (2) Steatorrhea
      (3) Diarrhea
   c. Gastrectomy (high subtotal or total)
      (1) Dumping syndrome
      (2) Malabsorption
      (3) Achlorhydria and lack of intrinsic factor
      (4) Hypoglycemia
   d. Intestinal resection
      (1) Jejunum
         (a) Decreased efficiency of absorption of many nutrients
      (2) Ileum
         (a) Vitamin B_{12} deficiency
         (b) Bile salt losses with diarrhea
         (c) Hyperoxaluria
      (3) Massive bowel resection
         (a) Life-threatening malabsorption
         (b) Malnutrition
         (c) Metabolic acidosis
      (4) Ileostomy and colostomy
         (a) Complications of salt and water balance
   e. Blind loop syndrome
   f. Pancreatectomy
      (1) Malabsorption
      (2) Diabetes mellitus

3. Chemotherapy treatment
   a. Corticosteroids
      (1) Fluid and electrolyte problems
      (2) Nitrogen and calcium losses
      (3) Hyperglycemia
   b. Antimetabolites, alkylating agents, and other drugs

*From Shils, M. E.: Nutrition and neoplasia. *In* Goodhart, R., and Shils, M., eds.: Modern Nutrition in Health and Disease. Philadelphia, Lea and Febiger, 6th ed., 1979. Reproduced with permission.

sensation ("mouth blindness") and xerostomia (dry mouth) consequent to decreased salivary secretion make chewing and swallowing difficult, combining to create a potentially serious situation since "the patients are not hungry anyway and it is easier to starve."[39] When all food becomes tasteless, appearance and aroma become much more important. Chewing and swallowing are assisted by use of gravies and salad dressings. Supplementary liquid formulas improve total intake.

Radiation to the lower neck and the mediastinum may induce esophagitis after several weeks of therapy but this usually disappears following cessation of therapy. Fibrosis with esophageal stricture may be a delayed effect.

Radiation damage to small and large bowel occurs in a small but significant number of patients receiving external and/or internal radiation therapy.[19] The epithelium of the small bowel is second only to bone marrow in its sensitivitiy to radiation. Altered intestinal function may occur during therapy and usually disappears. In those in whom significant "late" radiation changes develop, the symptoms recur usually within the year but sometimes not for 10 or more years. Flattening and ulceration of the mucosa, telangiectasis, fibrosis, endarteritis of small vessels and stenosis of the bowel develop and these changes are often progressive. Obstruction and fistula formation may occur and require bowel resection which complicates pre-existing diarrhea and malabsorption. While the damaged tissue may make surgery more difficult, the obstructive symptoms are often remediable; consequently, exploratory laparotomy is recommended before malnutrition increases the risk. In our experience, patients with severe radiation damage and previous resection are more difficult to manage than patients with massive small bowel resection alone. Intermittent obstruction, diarrhea, malabsorption, and chronic intestinal and bladder blood loss create a multitude of problems in nutrition and electrolyte balance. However, with close follow-up and attention to nutritional requirements utilizing enteral or parenteral routes of feeding, these patients often do very well.

Surgery

The effects of ablative surgery may be varied and many. Most of these procedures and their sequelae are, of course, not peculiar to surgery for cancer. However, certain resections are much more common or limited almost entirely to patients with cancer (e.g., extensive resection of the head and neck, total esophagectomy, total gastrectomy).

Surgery of the Head and Neck. Radical surgery of the head and neck region, including partial or total glossectomy and/or mandibulectomy, often interferes with mastication and swallowing. With some training or with laryngectomy, which prevents aspiration of fluids and food, oral food intake is possible. In others, prolonged tube feeding may be required. Patients can be taught to insert the nasopharyngeal tube themselves so that they avoid the psychological trauma and throat irritation associated with an indwelling tube. For those unable to pass the tube, its insertion with an esophagostomy or gastrostomy is recommended.

SURGERY OF THE DIGESTIVE TRACT. Esophagectomy often induces gastric stasis, diarrhea and significant malabsorption of fat.[56] The cause of these dysfunctions appears to be bilateral vagotomy inherent in the procedure; however, the precise intestinal mechanisms are unknown. Carbohydrate absorption is normal. The use of medium-chain triglycerides (MCT) as a major portion of fat intake diminishes the steatorrhea. Cholestyramine has been reported to reduce post-vagotomy diarrhea but supporting evidence is awaited.

GASTRECTOMY. The physiologic and nutritional consequences of subtotal and total gastrectomy have been reviewed elsewhere.[36] Clinical problems increase proportionately to the extent of the resection. In addition to the well-known occurrences of dumping syndrome, hypoglycemia, steatorrhea, afferent loop syndrome and loss of intrinsic factor, emphasis is needed on the long-term consequences of loss of the stomach with the insidious development of various vitamin and mineral deficiencies.[20, 28] Serious and persistent attention by the physician to prevent these nutritional problems is essential for long-term health when the underlying disease leading to the need for operation is benign, or when malignant disease has been eradicated.

INTESTINAL RESECTION. Clinical studies in normal subjects and in those with ablation of varying portions of small intestine indicate that all nutrients studied, with the exception of vitamin B_{12}, are most efficiently and (in the usual dietary amounts) rather completely absorbed in the proximal small bowel.[8] However, following jejunal resection, the ileum, with its reserve absorptive capacity, can absorb these nutrients in good degree if adequate nutritional status is maintained.

When the terminal ileum has been removed there will be poor absorption of both vitamin B_{12} and conjugated bile salts since this is the site of their physiologic absorption. Provision of vitamin B_{12} intramuscularly in doses of 100 mcg every month will prevent the development of vitamin B_{12} deficiency.

Failure to reabsorb conjugated bile salts will result in one of several problems. If the ileal resection is not extensive (usually less than 100 cm)[29] sufficient bile salts enter the large bowel to induce a brown water diarrhea which may be very distressing to the patient. Cholestyramine may be dramatically effective in controlling such a choleric diarrhea by its mechanism of binding bile salts. The capacity of the liver to synthesize sufficient new bile salts may be exceeded and the concentration of bile salts in the intestinal lumen becomes low, especially with successive meals. Consequently, fat absorption will be depressed and steatorrhea will ensure.[37] In such a situation, the patient will be helped by the feeding of a diet low in long-chain fats and use of medium-chain triglycerides which do not require bile salts for their absorption. The use of water-soluble forms of vitamin K and more of the other fat soluble vitamins is indicated to prevent deficiency of these nutrients. Sufficient polyunsaturated fats should be fed to assure adequate essential fatty acids.

Another consequence of ileal resection is hyperoxaluria and renal oxalate stone formation. This can be explained by the fact that the normal precipitation of oxalate ion by intestinal calcium ions is pre-

vented by a shortage of such free calcium ions because of their binding to fatty acids present in increased amounts in the remaining small bowel and colon by the steatorrheic ile-ectomized patients. The soluble oxalate is then absorbed in the colon and appears in the urine in increased concentrations with resultant probability of precipitation as calcium oxalate in the renal tubule.[18] On the basis of this explanation, reduced fat intake, together with an increased intake of calcium salts, appears advisable.

Massive small bowel resection, with a residual of three feet or less, presents very serious and long-term problems in maintaining adequate nutrition, including water and electrolytes. If there is some radiation damage of remaining bowel or loss of the ileocecal valve and portions of the colon the problems are intensified. However, the application of present knowledge with respect to care of these patients will often permit a successful outcome.[68, 72]

Pancreatectomy with consequent loss of digestive enzymes leads to loss into the stool not only of fats and of protein, but also of significant amounts of various vitamins and minerals. Since pancreatectomy necessitates partial gastrectomy, this is a complicating factor. The situation is further complicated by the fact that even subtotal pancreatectomy with anastomosis of the remaining portion of the pancreatic duct to the jejunum leads to a diabetic state in a significant proportion of patients.[53] Total pancreatectomy, of course, induces diabetes mellitus in all. The diabetic state occurring in conjunction with impaired carbohydrate, protein, and fat digestion further complicates the nutritional problems of such patients. The use of medium chain triglycerides and oligosaccharides may be beneficial.[53]

Pancreatic enzyme insufficiency may be effectively ameliorated by potent pancreatic extracts given with meals or at two hour intervals. Recent evaluations have been made of various pancreatic extracts,[17, 24] dosage schedules,[17, 41] and ancillary treatment such as antacids and an H_2 receptor antagonist.[48] Important factors are adequate dosage with meals and use of antacids or H_2 receptor antagonist when gastric secretion is normal or high since the latter may inactivate the pancreatic enzymes. Vitamin B_{12} absorption impaired by pancreatectomy may be improved by administration of pancreatic extract.[53] The diabetes mellitus following resection is usually of the "brittle" type, requiring relatively small amounts of insulin, and is rather difficult to control with precision. Hence, tolerance of some glycosuria is safer than the hypoglycemic episodes which may occur with achievement of glucose-free urine.

MAJOR HEPATIC RESECTION. The liver has a remarkable ability to regenerate by cellular hypertrophy and hyperplasia following massive resection. Immediate postoperative problems are met by glucose and albumin infusions and adequate replacement of electrolytes including phosphate.[53]

Chemotherapy

With the development of new drugs and understanding of their therapeutic applications, significant and, in some cases, dramatic im-

provement in the treatment of various forms of malignant disease has occurred. Most of the present chemotherapeutic agents, aside from hormones, inhibit one or more key steps in the intermediary metabolism of cells — normal as well as neoplastic — particularly those reactions involving the synthesis of purines, pyrimidines, DNA, and RNA.[10] Since the epithelial cells of the small intestine have a relatively rapid turnover, it is to be expected that many of these drugs will adversely affect intestinal functions to a degree depending upon the drug dosage, the duration of treatment, the rates of metabolism, and individual susceptibility.[46] The epithelium of the mouth and large bowel can also be affected, as well as other organs. Table 3 summarizes the effects these various agents may have on the alimentary tract. Adrenocorticosteroids which are commonly used in treatment of certain types of cancer have well known metabolic and nutritional effects which include depletion of nitrogen from muscle and loss of calcium and potassium from the body. These may be significant depending on the type of steroid used, dosage, and duration of treatment.

The frequent occurrence of resistance of malignant cells to a single drug, the realization of the need to kill the entire population of neoplastic cells in order to obtain a "cure," and improved understanding of the sites in DNA and RNA synthesis at which various chemotherapeutic agents have their effect have led to increasing use of multi-combination high-dose cyclical chemotherapy. These treatment programs, while increasingly effective against various malignant disease, also result in prolonged periods of anorexia and nausea because of their effects on the alimentary tract, with resulting impaired food intake. Since treatment may be prolonged, weight loss and progressive debility may be severe. These undesirable reactions are intensified when radiation therapy to the abdomen or surgery on the intestinal tract further decrease appetite or impair intestinal function. Adequate nutritional support makes a major contribution in permitting patients on these regimens to maintain weight and strength.

Table 3. *Effects of Cancer Chemotherapeutic Agents on the Alimentary Tract*†

DRUG	EFFECT*	DRUG	EFFECT
Adriamycin	A, N, V, N	Daunorubicin	A, N, V, M
Asparaginase	A, N, V	CDDP ("Cis-Pt")	A, N, V
BCNU	A, N, V	Hydroxyurea	N, V, M, D
Bleomycin	M	Methotrexate	A, N, U, P, M
Busulfan	N, V	Mithramycin	A, N, V, D
Cyclophosphamide	A, N, V, P	Procarbazine	A, N, U
Cytarabine	N, V, M, U	Vinblastine	N, V
Dactinomycin	A, N, V, D, M, P	Vincristine	P, O

†From Shils, M. E.: Nutrition and neoplasia. *In* Goodhart, R., and Shils, M., eds.: Modern Nutrition in Health and Disease. Philadelphia, Lea and Febiger, 6th ed., 1979. Reproduced with permission.

*A, Anorexia; N, Nausea; D, Diarrhea; M, Mucositis; P, Abdominal pain; O, Obstipation; U, Intestinal ulceration.

NUTRITIONAL THERAPY IN THE CANCER PATIENT

With the exceptions of certain leukemias, cancer has rarely been an acutely fatal disease. With the advent of more effective treatments it has become more and more a chronic or protracted illness and, consequently, a matter of concern for long periods for the patient and his physician. More successful palliation or potential "cure" of cancer is associated with requirement for variably longterm chemotherapy treatment schedules. Years must elapse before the patient and physician are willing to admit that the disease may be "cured." The physician and patient are faced, each in his own way, with the effects of the disease process, the psychological impact of its presence, and the long-term problems of treatment modalities and their side effects. These factors often combine to adversely affect the quality of life. When malnutrition is an additive factor, the problems are accentuated and there is increased morbidity and mortality. If the physician undertakes current treatment modalities, a sincere effort should be made to improve or maintain the quality of the life which makes for a reasonably comfortable and functioning individual. This concern about the patient's status should begin with the planning for the initial treatment and continue through to the hoped for long-term survival.

Various principles of nutritional therapy in the cancer patient have been presented.[140] These may be summarized here as follows:

1. Malnutrition is not an obligatory response of the host to cancer. It is relatively uncommon to find a patient with cancer whose nutritional status cannot be either maintained or improved by means of appropriate therapeutic nutritional modalities (i.e., oral, tube, or intravenous feeding).

2. A rational nutritional therapeutic program for a patient requires analysis of the factors inducing depletion in that patient. Every patient should have periodic assessments of nutritional status so that the already malnourished patients or those at risk of becoming malnourished are detected early.

3. Nutritional therapy should be instituted early when the patient is deemed to be at risk for malnutrition since it is much easier to maintain a reasonably good state of nutrition than it is to try to rehabilitate the already malnourished individual.

4. It is essential that the patient whose nutritional status has improved in the hospital be followed as an outpatient for assurance that the nutrition therapy program is not neglected after discharge.

5. Who is to be given aggressive nutritional therapy? If antitumor therapy of one type or another is to be undertaken, the patient deserves nutritional therapy so long as the treatment is applied and is being evaluated. If, on the other hand, the patient is not considered a suitable candidate for any further type of treatment, nutritional therapy is not to be stressed except in rare instances.

6. Nutritional therapy can be supportive, adjunctive, or definitive. *Supportive* therapy is exemplified by the patient with bowel obstruction who is deemed a poor surgical risk because of malnutrition and who will be clinically improved by nutritional means to the point

where surgery can be undertaken at appreciably lower risk. *Adjunctive* nutritional therapy is a part of the therapeutic program. Examples are: (a) improving resistance to infection by improving immune status; (b) permitting more rapid application and better adherence to a proposed antitumor therapeutic regimen by improved nutrition; or (c) inducing spontaneous closure of an intestinal fistula as a result of nutritional therapy. Nutrition therapy is defined as *definitive* when the therapy becomes the modality upon which the longer-term existence of the patient depends, i.e., when the nutritional program permits survival in good condition of a patient who has had a massive bowel resection or severe radiation enteritis or both and where debility or death will result without such therapy. This may be a short-time or long-term endeavor. The therapeutic modalities necessary to achieve these objectives should be available for inpatients and outpatients.

7. Nutritional status, tumor growth, and antitumor treatment are intimately related. Many of the most potent cytotoxic agents used in antitumor therapy have optimal activity against cells that are in the process of division. Hence, malignant lesions are most susceptible to chemotherapeutic measures where a high percentage of the cells are in that stage. Nutrition plays a role in the rate of cell growth and mitosis. Improved nutrition of experimental animals with transplanted tumors by mouth or by tube or by parenteral feeding[11, 13, 59] results in improved weight of the host. Tumor weight may increase proportionately[13, 59] or to a greater extent.[11] Clinical experience indicates it is a rare patient who has marked acceleration of growth of tumor during a period of improved nutrition. Increased residual tumor would be expected in patients as a result of improved nutrition since tumor cells have a dependency on good nutrition as do host cells. Furthermore, improved nutrition may be a therapeutically useful occurrence since actively dividing tumor cells are more likely, as stated above, to be more sensitive to radiation therapy and chemotherapy than are slowly dividing cells. It is the opinion of the author that it is not in the interest of the tumor-bearing patient who is a candidate for treatment to be carried on nutritional therapy without at the same time having adequate antitumor therapy.

REFERENCES

1. Allison, J. B., Wannemacher, R. W. Jr., Hilf, R., et al.: Dietary protein and tumor-host relationship in the rat. J. Nutr., *54*:593, 1954.
2. Ammann, R. W., Vetter, D., and Doyhle, P.: Gastrointestinal involvement in systemic mastocytosis. Gut, *17*:107, 1976.
3. Austed, W. I., Cornes, J. S., Gough, K. R., et al.: Steatorrhea and malignant lymphoma. Amer. J. Dig. Dis., *12*:475, 1967.
4. Barry, R. E.: Malignancy, weight loss and the small intestinal mucosa. Gut, *15*:562, 1974.
5. Baylin, S. B., Beaven, M. A., Engelman, K., et al.: Elevated histaminase activity in medulary carcinoma of the thyroid gland. New Engl. J. Med., *283*:1239, 1970.
6. Begg, R. W., and Dickinson, T. E.: Systemic effects of tumors in force-fed rats. Cancer Res., *11*:409, 1951.

7. Benson, G. D., Kowlessar, O. D., and Sleisenger, M. H.: Adult coeliac disease with emphasis upon response to gluten free diet. Medicine, *43*:1, 1964.
8. Booth, C. C.: The metabolic effects of intestinal resection in man. Postgrad. Med. J., *37*:725, 1961.
9. Bossak, E. T., Wang, C. L., and Adlersberg, D.: Clinical aspects of the malabsorption syndrome (idiopathic sprue). J. Mt. Sinai Hosp., N.Y. *24*:286, 1957.
10. Calabresi, P., and Parks, R. E. Jr.: Chemotherapy of neoplastic disease. *In* Goodman and Gilman, eds: Pharmacological Basis of Therapeutics. New York, MacMillan, 5th ed., 1975, pp. 1248–1307.
11. Cameron, I. L., and Pavlet, W. A.: Stimulation of growth of a transplantable hepatoma in rats by parenteral nutrition. J. Natl. Cancer Inst., *56*:597, 1976.
12. Da Cruz, G. M. G., Gardner, J. D., and Peskin, G. W.: Mechanism of diarrhea of villous adenomas. Amer. J. Surg., *115*:203, 1968.
13. Daly, J. M., Copeland, E. M., and Dudrick, S. J.: Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery, *84*:655, 1978.
14. Deveney, C. W., Deveney, K. S., and Way, L. W.: The Zollinger-Ellison syndrome — 23 years later. Ann. Surg., *188*:384, 1978.
15. De Wys, W.: Working conference on anorexia and cachexia of neoplastic disease. Cancer Res., *30*:2816, 1976.
16. De Wys, W. D., and Walters, K.: Abnormalities of taste sensation in cancer patients. Cancer, *36*:1888, 1975.
17. DiMagno, E. P., Malagelada, J. R., Go, V. L. W., et al.: Fate of orally ingested enzymes in pancreatic insufficiency. New Engl. J. Med., *296*:1318, 1977.
18. Dobbins, J. W. and Binder, H. J.: Importance of the colon in enteric hyperoxaluria. New Engl. J. Med., *296*:298, 1977.
19. Donaldson, S. S.: Nutritional consequences of radiotherapy. Cancer Res., *37*:2407, 1977.
20. Eddy, R. L.: Metabolic bone disease after gastrectomy. Amer. J. Med., *50*:442, 1971.
21. Ehrlich, A. N., Stalder, G., Geller, W., et al.: Gastrointestinal manifestations of malignant lymphoma. Gastroenterology, *54*:1115, 1968.
22. Eidelman, S., Parkins, R. A., and Rubin, C. E.: Abdominal lyphoma presenting as malabsorption. Medicine, *45*:111, 1966.
23. Gough, K. R., Read, A. E., and Naish, J. M.: Intestinal reticulosis as a complication of idiopathic steatorrhea. Gut, *3*:232, 1962.
24. Graham, D. Y.: Enzyme replacement therapy of exocrine pancreatic insufficiency in man. New Engl. J. Med., *296*:1314, 1977.
25. Gray, T. K., Bieberdorf, J. A., and Fordtran, J. S.: Thyrocalcitonin and the jejunal absorption of calcium, water and electrolytes in normal subjects. J. Clin. Invest., *52*:3084, 1973.
26. Hall, C. A., and Finkler, A. E.: Measurement of the amounts of the individual vitamin B_{12} binding proteins in plasma. II. Abnormalities in leukemia and pernicious anemia. Bllod, *27*:618, 1966.
27. Harris, O. D., Cooke, W. T., Thompson, H., et al.: Malignancy in adult coeliac disease and idiopathic steatorrhea. Amer. J. Med., *42*:899, 1967.
28. Hines, J. D., Hoffbrand, A. V., and Mollin, D. L.: The hematologic complications following partial gastrectomy. A study of 292 patients. Amer. J. Med. *43*:555, 1967.
29. Hofmann, A. F., and Poley, J. R.: Cholestyramine treatment of diarrheas associated with ileal resection. New Engl. J. Med., *281*:397, 1969.
30. Holyroyde, C. P., Gabuzda, T. G., Putnam, R. C., et al.: Altered glucose metabolism in metastatic carcinoma. Cancer Res., *35*:3710, 1975.
31. Jasani, B., Donaldson, J., Ratcliffe, J. G., et al.: Mechanism of impaired glucose tolerance in patients with neoplasia. Brit. J. Cancer, *38*:287, 1978.
32. Jones, A., Krishnan, C., and Forstner, G.: Pathogenesis of mucosal injury in the blind loop syndrome: release of disaccharidases from brush border membranes by extracts of bacteria obtained from intestinal blind loops in rats. Gastroenterology, *75*:791, 1978.
33. Kleeman, C. R.: Hypo-osmolar syndromes secondary to impaired water excretion. Ann. Rev. Med., *21*:259, 1970.
34. Klipstein, F. A., and Smarth, G.: Intestinal structure and function in neoplastic disease. Amer. J. Digest. Dis., *14*:887, 1969.
35. Kowlessar, O. D., Law, D. H., and Sleisenger, M. H.: Malabsorption syndrome associated with metastatic carcinoid tumor. Amer. J. Med., *27*:673, 1959.
36. Lawrence, W., Jr.: Nutritional consequences of surgical resection of the gastrointestinal tract for cancer. Cancer Res., *37*:2379, 1977.
37. LeRusso, N. F., Korman M. G., Hoffman, N. E., et al.: Dynamics of the enterohepatic circulation of bile acids. New Engl. J. Med., *291*:689, 1974.

38. Liddle, G. W., Givens, J. R., Nicholson, W. E., et al.: The ectopic ACTH syndrome. Cancer Res., 25:1057, 1965.
39. MacCarthy-Leventhal, E. M.: Post-radiation mouth blindness, Lancet, 2:1138, 1959.
40. Magnus, E. M.: Folate activity in serum and red cells of patients with cancer. Cancer Res., 27:490, 1967.
41. Meyer, J. H.: The ins and outs of oral pancreatic enzymes (editorial). New Engl. J. Med., 96:1347, 1977.
42. Milder, J. W., ed.: Conference on nutrition and cancer. Cancer Res., 37:2325–2471, 1977.
43. Modlin, I. M., Bloom, S. R., and Mitchell, S. J.: Experimental evidence for vasoactive intestinal peptide as the cause of the watery diarrhea syndrome. Gastroenterology, 75:1051, 1978.
44. Morrison, S. D.: Origins of anorexia in neoplastic disease. Amer. J. Clin. Nutr., 31:1104, 1978.
45. Novis, B. H., Banks, S., Marks, I. N., et al.: Abdominal lymphomas presenting as malabsorption. Quart. J. Med., 40:521, 1971.
46. Ohnuma, T., and Holland, J. F.: Nutritional consequences of cancer chemotherapy and immunotherapy. Cancer Res., 37:2395, 1977.
47. Pearse, A. G. E., Polak, J. M., and Bloom, S. R.: The newer gut hormones: cellular sources, physiology, pathology and clinical aspects. Gastroenterology, 72:746, 1977.
48. Regan, P. T., Malagelada, J. R., diMagno, E. P., et al.: Comparative effects of antacids, cimetidine and enteric coating on the therapeutic responses to oral enzymes in severe pancreatic insufficiency. New Engl. J. Med., 297:854, 1977.
49. Rose, D. P.: Folic acid deficiency in leukemia and lymphomas. J. Clin. Patho., 19:29, 1966.
50. Sandler, M., Karim, S. M. M., and Williams, E. D.: Prostaglandins in amine-peptide-secreting tumours. Lancet, 2:1053, 1968.
51. Schimke, R. N., Hartman, W. H., Prout, T. E., et al.: Syndrome of bilateral pheochromocytoma, medullary thyroid and carcinoma and multiple neuromas. New Engl. J. Med., 279:1, 1968.
52. Schwartz, M. K.: Role of trace elements in cancer. Cancer Res., 35:348, 1975.
53. Shils, M. E.: Effects on nutrition of surgery of liver, pancreas and genitourinary tract. Cancer, 37:2387, 1977.
54. Shils, M. E.: Nutritional problems associated with gastrointestinal and genitourinary cancer. Cancer Res., 37:2366, 1977.
55. Shils, M. E.: Principles of nutrition therapy. Cancer, May 1979 (in press).
56. Shils, M. E.: The esophagus, the vagi and fat absorption. Surg. Gynec. Obstet., 132:709, 1971.
57. Shimoda, S. S., Saunders, D. R., and Rubin, C. E.: The Zollinger-Ellison syndrome with steatorrhea. II. The mechanism of fat and vitamin B_{12} malabsorption. Gastroenterology, 55:705, 1968.
58. Spray, G. H., and Witts, L. J.: The utilization of folic acid in anaemia and leukaemia. Clin. Sci., 12:385, 1953.
59. Steiger, E., Oram-Smith, J., Miller, E., et al.: Effects of nutrition on tumor growth and tolerance to chemotherapy. J. Surg. Res., 18:455, 1975.
60. Tashjian, A. H. Jr. and Melvin, K. E. W.: Medullary carcinoma of the thyroid gland. Studies of thyrocalcitonin in plasma and tumor extracts. New Engl. J. Med., 279:279, 1968.
61. Theologides, A.: The anorexia-cachexia syndrome: a new hypothesis. Ann. N. Y. Acad. Sci., 230:14, 1974.
62. Toskes, P. P., Hansell, J., Cerda, J., et al.: Vitamin B_{12} metabolism in chronic pancreatic insufficiency. New Engl. J. Med., 284:627, 1971.
63. Verner, J. V., and Morrison, A. B.: Endocrine pancreatic islet disease with diarrhoea. Arch. Intern. Med., 133:492, 1974.
64. Wolman, S. C., Anderson, G. H., Marliss, E. B., et al.: Zinc in total parenteral nutrition: requirement and metabolic effects. Gastroenterology, 76:458, 1979.
65. Waldman, T. A., Broder, S., and Strober,: Protein-Losing enteropathies in malignancy. Ann. N. Y. Acad. Science, 230:306, 1974.
66. Warmold, I., Lundholm, K., and Schirsten, T.: Energy balance and body composition in cancer patients. Cancer Res., 38:1801, 1978.
67. Waterhouse, C., and Kemperman, J. H.: Carbohydrate metabolism in subjects with cancer. Cancer Res., 31:1273, 1971.
68. Weser, E.: The management of patients after small bowel resection. Gastroenterology, 71:146, 1976.
69. Williams, E. D., Karim, S. M. M., and Sandler, M.: Prostglandin secretion by medullary carcinoma of the thyroid. Lancet, 1:22, 1968.

70. Williams, L. R., and Cohen, M. H.: Altered taste thresholds in lung cancer. Amer. J. Clin. Nutr., 31:122, 1978.
71. Wilmore, D. W.: The Metabolic Management of the Critically Ill. New York, Plenum, 1977.
72. Wilmore, D. W., Dudrick, S. J., Daly, J. M., et al.: The role of nutrition in the adaptation of the small intestine after massive resection. Surg. Gynec. Obstet., 132:673, 1971.
73. Young, V. R.: Energy metabolism and requirements in the cancer patient. Cancer Res. 37:2336, 19 77.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

Diet and Nutrition as Modifying Factors in Tumor Development

*Maurice E. Shils, M.D., Sc.D.**

Observations from experiments with animals, epidemiologic data, and some experimental data in man have progressed and brought us to the point at which it is pertinent for a physician to ask how he should respond to his patient who asks, "What diet should I and my family have in order to try to prevent the development of cancer?" As little as ten years ago this question was rarely asked by physicians or patients. The widespread recent publicity given to the subject in the lay press as well as in the medical literature makes this an appropriate question now.

It should be stated at the outset that one cannot extrapolate with assurance from animal studies to man and much of the epidemiologic data are sufficiently conflicting to warrant caution in making many generalizations. Nevertheless, the potential public health and personal importance of the subject suggest that a review of data and an expression of opinion on some aspects are warranted.

CALORIC INTAKE

Animal experimental studies initiated by Tannenbaum many years ago provide strong evidence that restriction of total caloric intake decreases the development of spontaneous tumors and also inhibits growth of either spontaneously developing or transplanted tumors.[60] More recent long term studies confirm and extend these findings. Within each dietary group of rats on a lifetime experiment, regardless of the composition of the diet, rats of heavier weight had a greater risk of developing tumors than lighter animals, and body weight of the rats early in life correlated directly with tumor prevalence in later life.[58, 59] Even relatively short term restriction of food intake by rats after weaning followed by ad libitum regimens substantially reduced the prevalence and long term growth of neoplasms. While serious restriction of

* Associate Professor of Medicine, Cornell University Medical College; Attending Physician, and Director of Clinical Nutrition, Memorial Sloan-Kettering Cancer Center, New York, New York

caloric intake may not be practical in man, an effort to prevent overweight in childhood and in later life seems indicated.

NUTRIENTS AS INHIBITORS AND MODIFIERS OF CARCINOGENS

There is increasing evidence that chemical carcinogens account for an increasing proportion of cancer in human beings. Any maneuver that will prevent the exposure of susceptible cells to carcinogens has potential protective value. Carcinogens have a common reactive form, namely, a positively charged electrophilic species which binds to macromolecules. Carcinogens are converted to such active forms by one or more reactions.[46] Various mechanisms for the prevention of chemical carcinogenesis are known.[69] Much of the presently available information comes from empirical studies, however, and the mechanism of action of many agents is thus still uncertain. If inhibitors of chemical carcinogenesis are to have any practical value, they will have to be substances of little or no toxicity. Hence, there is special interest in certain dietary or nutritional factors as possible protective mechanisms. Groups of compounds of interest which are considered briefly here include those that (a) alter (usually increase) drug-metabolizing (microsomal oxidase) enzymes; these have maximum effectiveness when administered 24 to 48 hours prior to the challenge by a carcinogen; (b) act as antioxidants which are inhibitory when administered shortly before the carcinogen, (c) prevent formation of the carcinogen, and (d) reverse the early stages of the carcinogenic activity.

Carcinogens or their antecedents can be inhaled, or may be consumed as preformed or procarcinogens from food or water. Antecedents are converted to active carcinogens in the intestinal tract by the action of bacteria, and procarcinogens are converted to carcinogens as a result of metabolism after absorption. Certain dietary components may either increase or decrease the absorption of such agents.

Dietary Factors as Inducers of Drug Metabolizing Enzymes

Endoplasmic reticulum of various organs, especially the liver, contains enzyme systems which can convert many drugs and foreign chemicals into polar compounds.[10] Administration of certain drugs or agents to an experimental animal or to man induces these enzyme systems, increasing the capacity of the organism to metabolize a wide range of such drugs or chemicals. Many chemical carcinogens are among the wide variety of xenobiotic compounds that can be metabolized by these enzymes.[11] While drug and developmental factors play a role in the inducibility of these enzymes, nutritional factors are also influential. The activities of these enzymes may be depressed by starvation, protein deficiency, fat and carbohydrate modification, and certain mineral and vitamin deficiencies.[7]

The effects of dietary factors on the activities of microsomal oxidase enzymes of the small intestine and lung have been studied in experimental animals. It has been suggested that the presence of these drug-metabolizing enzymes in the major portals of entry of food and air protect against the entry of carcinogens by these routes. Induction of these enzymes protects against a number of chemical carcinogens.[68] It has been found that most, if not all, of the enzyme activity in the intestines and lungs have resulted from exposure to exogenous inducing agents present in foods. Either starvation or the feeding of purified diets to the animals led to total loss of the ability to hydroxylate aromatic polycyclic hydrocarbons.

Efforts to identify the chemical nature of the enzyme-inducers present in natural foods revealed that the most potent sources were vegetables of the Brassicaceae family which includes Brussels sprouts, cabbage, and broccoli, from which various indoles with inducing activity were isolated.[69] Other inducers of these enzymes have afforded protection against polycyclic hydrocarbons (which are toxic), flavones (which have little toxicity), barbiturates, and phenothiazines.[68, 69] While the increased activity of these enzymes is protective because they inactive primary carcinogens, it has been shown that they may also metabolize carcinogen precursors into active forms. However, Wattenberg has suggested that such activation of precarcinogens to proximate carcinogens is not likely to increase carcinogenesis.[69]

Nutrients as Inhibitors of Carcinogens

The use of antioxidants as possible inhibitors of chemical carcinogens has been based on the concept that the compounds may exert an inactivating effect on the reactive species of carcinogens. While publicity has been given to the possible role of vitamin E (alpha tocopherol), the published results are so variable that their potential value is not clear.

In the mouse and rat, phenolic oxidants and particularly butylated hydroxyanisole (BHA) butylated hydroxytoluene (BHT), and several nonphenolic antioxidants have been shown to inhibit the expected carcinogenesis of a variety of compounds. BHA is of interest because of its extensive use as an additive in food for human consumption. Wattenberg has estimated that human consumption of this compound may be important in inhibiting the effects of chronic exposure to low doses of carcinogen.[69] There are other nonphenolic antioxidants which are used commercially in animal feeds or are found as constituents of edible plants which also may inhibit the development of carcinogens.

The evidence to date is still inadequate to suggest that inhibitors of carcinogenesis should be deliberately added to food or ingested in other forms for this purpose. However, the day may not be far off when such additives may be indicated, particularly in individuals who have increased exposure to certain potential carcinogens.[69]

The potential role of nitrosamines as carcinogenic, mutagenic, and cytotoxic agents has focused attention on the sources of their precur-

sors. Nitrite ion reacts with naturally occuring and synthetic secondary and tertiary amines to form nitroso compounds. Nitrites and nitrates from food and water are of current concern. The findings that ascorbic acid reacts very rapidly with nitrite and effectively competes with amines for nitrite[48] suggested that administration of ascorbic acid with potentially nitrosatable drugs and nitrite-containing foods may reduce the hazards associated with the ingestion of these substances. Ascorbic acid has been reported to inhibit tumor induction in rats given nitrite with urea or amines or with N-nitroso compounds[47] and to decrease the formation of methylnitrosourea in foods incubated in vitro under simulated gastric conditions.[70]

Nutrients in the Reversal of Early Carcinogenic Effects

Vitamin A and related compounds have assumed increased interest as potential protective agents that act by reversing early carcinogenic effects. Vitamin A is of special interest because of its fundamental role in epithelial cell differentiation. While the vitamin A status does not influence the response to all carcinogens in the same manner, it has been found that vitamin A deficient rats are more susceptible than controls to induction of colonic cancer by aflatoxin B_1[57] and to tumors of the respiratory tract[49] and bladder.[50] The potential protective effect of topical or systemic administration of common forms of vitamin A has been tested by various investigators who have used it to inhibit the action of various carcinogens in experimental animals.

The common forms of vitamin A esters have limitations as antitumor agents in pharmacologic doses either because their metabolic pathways limit their availability to specific target sites (e.g., bladder epithelium) or because of their toxicity.[62] Accordingly, Sporn and associates have developed synthetic analogs (retinoids) which are less toxic and have different patterns of tissue distribution, metabolism, and storage.[62] Preliminary evidence for the value of specific retinoids in the epithelial cancer in experimental animals is emerging. Such retinoids are undergoing clinical trial as preventives against certain human tumors.

Experimental Studies With Other Specific Nutrients

A large and rapidly growing body of literature gives strong support to the concept that the presence or absence of certain nutrients can strongly influence the effects of carcinogens. Years ago, for example, it was shown that deficiency of riboflavin and protein will result in the development of liver cancer in rats given the dye butter yellow (p-dimethylaminoazobenzene). It is now known that riboflavin is a constituent of an enzyme which splits this dye and inactivates it. Hence, a deficiency of riboflavin causes persistence of the carcinogen and its potential for interaction with DNA. It has also been found that deficiency of lipotropic agents will increase the carcinogenicity of aflatoxins, and a deficiency of protein will increase that of dimethylnitrosamine.[57] Increased amounts of dietary fat tend to promote tumor

development on exposure to certain carcinogens, particularly those inducing mammary and colinic cancers. While the type of fat (i.e., saturated or unsaturated) does not seem to have much effect on the induction of colon cancer by carcinogens such as dimethylhydrazine, there is evidence that mammary tumors develop to a greater degree in animals fed polyunsaturated fat as compared to those fed the same amount of saturated fat.[8] Further studies in this intriguing area are obviously necessary.

Bile salts fed either alone or with cholestyramine (a nonabsorbable resin which increases entry of bile salts into the colon) or cholestyramine alone increases the colon tumor-producing effect of certain carcinogens. It has been reported recently that cholesterol at 6 to 9 mg per day added to a complete low-fat liquid formula markedly decreased the time of appearance of colon cancer in rats injected with dimethylhydrazine as compared to that occurring with the same formula without added cholesterol.[14] These and other studies including the effects of dietary deficiency on transplanted tumors have been reviewed recently.[51, 61]

NUTRITIONAL STATUS AND IMMUNE RESPONSES

Depressed cellular immunity is fairly common in cancer patients and, in the past, has frequently been attributed to the effects of cancer per se. Studies done initially in malnourished children[64] and adults[43] and in cancer patients[12] have shown that immune responses can be altered by malnutrition. Malnutrition also induces altered phagocytosis, and macrophage activity and depressed complement levels.[64] Efforts have been made to improve immunity either by improving nutritional status or, alternatively, by inducing certain deficiencies in an effort to slow tumor growth and enhance immune responses.[10]

A major problem is the apparent inability of the host immune defenses to recognize a cancer cell in all instances. In animal experiments, when the growth of a specific tumor is delayed by the induction of a deficiency such as that of riboflavin, immune defenses become effective and the tumor regresses.[39] On the other hand, production of blocking antibody can prevent destruction of tumor cells. It has been suggested that certain deficiencies may inhibit formation of blocking antibody without depressing cellular immunity.[40] Deficiencies of certain amino acids have been reported to depress hemagglutinating and blocking antibody responses without affecting cytotoxic and cell-mediated immunity.[41] There is contradictory evidence for the effect of certain amino acid deficiencies on the growth of transplanted tumors.[66, 73]

Copeland and associates have studied the effects of nutritional depletion and rehabilitation on immune competence, tumor growth, and responses to antitumor therapy.[12] Their data indicate that malnutrition leads to immunosuppression as well as do surgery, radiation therapy,

and chemotherapy. The majority of patients who, on initial testing, gave a negative response to various intradermal antigens had positive results (i.e., had increased cellular immunity) to skin testing following nutritional treatment with total parenteral nutrition despite chemotherapy and surgery. Radiation therapy, on the other hand prevented or reversed the improved immune responses. Experimental studies with tumor-bearing rats with depressed cellular immunity induced by protein deficiency also responded to nutritional repletion with return of their immunity.[15] In an uncontrolled clinical study, responses to chemotherapy occurred only in those patients who had positive skin tests.[12] There is increasing clinical evidence that re-establishment of cellular immunity by nutritional means and adequate control of infection play an important role in decreasing morbidity and mortality in surgical patients.[53]

The importance of insuring optimum defense against infection in the cancer patient emphasizes the need for providing adequate nutrition.

HUMAN EPIDEMIOLOGIC DATA RELATING NEOPLASTIC DEVELOPMENT TO DIETARY PRACTICES

From the earliest medical records to the present, physicians and laymen have postulated an association (either protective or predisposing) between diet and the development of cancer.[36] This has proved a fertile area for a wide range of speculation extending from food fadists to epidemiologists and now to experimental scientists. The role of diet as an important environmental variable has gained increasing attention as epidemiologic studies have associated differences in diet composition with regional differences in prevalence of types of cancer.

Epidemiologic surveys have indicated (a) marked differences in the prevalence of malignant lesions originating in different organ systems within a given population, (b) variations in the prevalence of malignant disease in a specific organ among different populations which may or may not be geographically distant, and (c) changes in prevalence of certain cancers associated with migrating populations. Such data suggest that environmental factors are important, even though they do not prove the identity of such factors. Increasing attention has also focused on food contaminants as possible etiologic factors in human cancer since the discovery that *Aspergillus flavus*, which grows on various foods under suitable conditions, produces the very potent liver carcinogen, aflatoxin.

Possible etiologic interrelations of a number of factors and their variations in various geographic areas have been reviewed.[2, 31, 5] Caution in interpretation of epidemiologic information is necessary since differences in the intake of a given dietary constituent (e.g., fat or carbohydrate) among population groups must be associated, by the nature of diet composition, with reciprocal differences in intakes of other essential nutrients and food constituents. The differences in tumor in-

cidence, although ascribed to variations in a specific dietary constituent, may actually result from other factors. Furthermore, differences in diet are often associated with major differences in living standards and other environmental conditions. Such complexity should lead to caution and the development of more precise evidence before ascribing non-causative associations to "proven" etiologic factors.

Gastrointestinal neoplasms have been of special interest, since the prevalence of malignant disease in the upper and the lower areas of the alimentary tract is often high in certain areas and the survival rate is often low. There is increasing evidence that development and clinical expression of human alimentary tract carcinoma may run a course of many years. Thus, the initiating factors may not necessarily be present at the time of the epidemiologic survey. This creates difficulty in obtaining accurate retrospective individual data. Studies of migrant populations with those populations who have remained in the original site permit a more objective evaluation of environmental differences, including the effects of time, age, and generation.

Oropharyngeal and Esophageal Carcinoma

An association has been noted between the occurrence of the Plummer-Vinson syndrome (sideropenic anemia with epithelial lesions) and cancer of the hypopharynx in Swedish women.[42] This syndrome is believed to be secondary to iron deficiency, but vitamin deficiencies may also be involved. There is a decreasing trend in the incidence of both the syndrome and the cancer in association with improved nutrition and health care.[42] Esophageal carcinoma has a world wide incidence which varies more than 100 fold.[16] Increased use of alcohol and tobacco has been associated with esophageal cancer in New York City and certain parts of Brittany and Normandy, with a much higher prevalence among males. However, in other areas alcohol and tobacco do not appear to be factors of major importance. Poor economic groups appear to be more affected by this type of cancer.

Gastric Cancer

There has been a steady downward trend in the prevalence of stomach cancer in the United States for more than 30 years, so that now rates are now only one half to one fifth their maximum since 1935.[17] Similar downward trends have become apparent in Western Europe and more recently in Japan, particularly in large city populations.[35] Negative correlations have been found between the prevalence of gastric cancer and total fat consumption (and, hence, with living standard and meat consumption) and positive correlations noted with fish consumption. However, these relations are dependent on situations in specific countries and hence are questionable. Despite claims, there is no consistent correlation of gastric cancer with the use of smoked fish or meat. It is the opinion of the author that no food has been identified that is common to all high risk populations.

There is frequent reference to the possible roles of nitrites in induction of cancer, particularly that of the stomach. Nitrite enters the

food supply from nitrate in food or in water or as preformed nitrite. Nitrate in considerable amounts was used in the United States as a food preservative especially for fish and meat prior to the widespread advent of refrigeration. In recent years use of the substance for this purpose has decreased. Nitrates from fertilizer offer a potential risk since they are ingested in agricultural products and well water. Approximately 86 per cent of ingested nitrate in the American diet is derived from vegetables.[71] It is known that nitrate is reduced to nitrite by various microbial species during storage of food at room temperature — but not in the refrigerator — and that normal oral microbial flora in man can reduce nitrate to nitrite which appears in the saliva. It has been found that the mean nitrite concentration in the gastric juice of patients with pernicious anemia (who have an increased risk for gastric cancer) is nearly 50 times that of age-matched normal controls.[60] Nitrite is also formed by bacterial action in the large bowel. The FDA concentrations of nitrite used to preserve meats and fish to inhibit the spores of *Clostridium botulinum* are usually less than 200 parts per million.[38]

There has been increased interest in this subject with the report of Newberne to the effect that nitrites added to food increased the incidence of lymphomas in rats.[50] While the evidence for a causative effect of nitrite for induction of gastric cancer in man is circumstantial, the associations mentioned suggest that efforts be made to reduce nitrite and nitrate intake without at the same time increasing the risk of botulinum infection. It has been mentioned above that ascorbic acid reacts with nitrite to inhibit the formation of nitrosoamines. Other compounds such as erythorbate, phenolic compounds used in curing smoke, gallic acid, cysteine, and sodium sulfite act similarly.

Colon Cancer

When colon and rectal carcinomas are considered together they are the most frequently diagnosed cancer by site in the United States with the exception of skin cancer;[17] hence, the increasing attention to early diagnosis and efforts at prevention of this type of cancer. Death rates for these cancers in a number of countries have a strong negative correlation with those of gastric cancer. Colorectal cancer has an appreciably higher incidence in economically developed countries with the outstanding exception of Japan and to a lesser degree Finland.[13, 74] The ratio of colon to rectal cancer (C/R ratio) is continuously increasing in Japan, and the C/R ratio has a reverse association with the quantity of rice ingested per day.[35] The association of colon cancer with environment has been strengthened by observed changes following migration from a country to low risk to one of high risk. A striking example is the progressive increase in mortality from colon cancer in Japanese born and living in Japan, those migrating to Hawaii (Issei), and those of Japanese descent born in Hawaii (Nisei).[13] Similar trends have been noted in Japanese in California and Puerto Ricans living on the island as compared to those in the continental United States. Con-

trary to the decline in gastric cancer, which does not express itself clearly until the first generation born to immigrants coming from high risk areas, the increase in large bowel cancer is seen in the immigrant generation. The observation indicates a strong environmental influence expressing itself clearly in a matter of 10 years or so.

This strong environmental association has led to increasing numbers of epidemiologic and experimental studies attempting to delineate the roles of dietary and nutritional influences. Wynder and associates have emphasized the worldwide correlation among colon cancer, fat consumption, and myocardial infarction.[71] Armstrong and Doll found that the environmental variables most highly correlated with colon cancer are meat and animal protein consumption; while there is a high correlation with total fat, control of other variables reduces the correlation coefficient for total fat to rather low levels.[2] Patterns of food consumption are such that meat, animal protein, and fat consumption are highly correlated with one another.

There are differences among epidemiologic findings with respect to prevalence of cancer and patterns of food consumption. For example, beef consumption is lower in the Northeastern than in the Central or the Western states; however, colon cancer is more prevalent in the Northeast.[4] Although mortality from colon cancer is appreciably lower among both Mormons and non-Mormons in Utah than in the United States as a whole, dietary surveys found little difference in meat, fat, and fiber consumption.[45] Exception has been taken to the hypothesis that beef and fat consumption are involved in the etiology of colorectal cancer in the United States.[23] Furthermore, it has been suggested recently that there is a negative or no correlation between animal fat intake and bowel cancer, but a positive correlation with total fat and vegetable fat.[22] Most of the epidemiologic studies which have compared patients with cancer of the large bowel with control subjects have failed to demonstrate a clear association between the cancer and meat or fat consumption with the exception of a study indicating a positive association with beef and bean consumption in Hawaiian Japanese.[29] The latter are exceptional since they have considerable dietary heterogeneity based on previous ethnic practices and generational differences.

Assuming that fat is an etiologic factor, what is the metabolic action that could induce malignant disease? An hypothesis has been advanced to the effect that "Western" type diets have two complementary effects: (1) they increase bile secretion over that of diets low in fat and (2) they induce a type of colonic flora with an increase of anaerobes and the presence of certain strains of clostridia capable of converting bile acids by dehydrogenation into actual or potential carcinogens.[33] Significant differences have been reported in the fecal flora between high and low risk groups subsisting on Western and vegetarian diets respectively,[33] in the content of fecal sterols,[33, 55] and in volunteers alternating from high meat to low meat diets.[54] It has been claimed that patients with colon cancer had increased amounts of fecal bile acids[34, 56] and dehydrogenating clostridia[34] and increased fecal bacterial 7-alpha-dehydroxylation of primary bile acids as com-

pared to control subjects.[50] However, there are also reports which indicate only relatively few or no statistical differences in fecal flora in studies of individuals on Japanese and western type diets[21] between Seventh-Day Adventists (who abstained from smoking and drinking, use of coffee, tea, and certain condiments, and 50 per cent of whom follow lacto-ovovegetarian diets,[52]) and those individuals on a usual American type diet[26] or between vegetarian and non-vegetarian Seventh-Day Adventists.[24] No differences have been noted in cancer mortality between physicians who are Seventh-Day Adventists and those who are non-Adventists; this suggests the role of selection factors.[52]

Since the fecal flora of man include a large number of species, a serious approach to quantitative analysis requires precise and sophisticated methods of collection and bacteriologic examination. Finegold and associates[24] found approximately 150 different fecal bacterial species or subspecies. In comparing the flora between populations at high or low risk for colon cancer, they found significant differences for 21 organisms or groups of organisms, but the clinical significance of these differences remains to be proven. Further research is necessary to clarify the etiologic pertinence of various postulated factors.

Another hypothesis which has aroused interest and has led to active experimentation suggests an inverse relation between intake of non-digestible polysaccharides ("fiber") and large bowel cancer.[5, 6] There are counter-claims to the basis of the original hypothesis relating fiber and bowel transit time to colon cancer. Variations and negative correlations have been found among transit times in different populations consuming diets with differing of fiber.[26, 27, 30]

The reported epidemiologic correlations among fat and meat consumption, fiber intake, and colorectal cancer have led to increasing recommendations for consumption of a "prudent diet" similar to that suggested by Jolliffe and associates many years ago in an effort to reduce atherosclerosis. Such a diet involves moderate restriction of calories and animal fat, a higher ratio of polyunsaturated to saturated fats, and increased use of vegetables and cereals. This author takes the position that the relation of specific dietary components to cancer of the colon in man is unsettled at present although there is an increasing claim that a "typical" American type diet is not optimal for prevention of this type of cancer. The impressive and progressive decline in deaths from myocardial infarction since about 1963 provides the most potent argument for a "prudent diet" and seems justification enough for recommending such a diet. This may prove to be beneficial also with respect to minimizing the development of colorectal cancer.

Hormone-Dependent Cancers

These include malignant lesions of the breast, endometrium, testis, ovary, prostate, and thyroid. The relation of cancer of the thyroid to iodide deficiency is well established and will not be discussed here. There is fairly good correlation in many but not all areas between the incidence rates for large bowel cancer and for those of

breast, endometrium, ovarian, testicular and prostatic cancers in declining order.[3] As with large bowel cancer, a shift in the prevalence of breast cancer to the pattern of the host country has been shown for Poles migrating to the United States and Australia and for Japanese residents in the United States. The changes manifest themselves clearly in the children of the migrants suggesting that environmental effects play a key role in relatively early life. In the case of breast cancer this would be the time of puberty and breast development.

There is a high correlation between fat consumption and mortality not only for carcinomas of the breast but also for those of the body of the uterus, ovary, prostate, and testis.[2] The positive correlation with fat consumption for both bowel and endocrine-dependent tumors must be viewed in the context of the socioeconomic factors, the type of fats consumed, body stature, and genetic differences, and the adequacy of the dietary surveys. Differences in weight and height among women 45 to 50 years and older with breast cancer in two Dutch cities and in Aichi Prefecture in Japan suggest that approximately 50 per cent of the differences in incidence between these two regions are attributable to differences in body weight and height.[18] Similar differences for postmenopausal women hold when prevalence of cancer is plotted against body surface area.

Nutrition may play a role in the development of breast cancer by way of modification of hormones since these can be altered by dietary means.[25] Endocrine profiles of young Japanese women living in Hawaii have become more similar to those of Caucasian women than to those of women in Japan.[19]

Carcinoma of the endometrium is highly correlated with total fat consumption as indicated above. Reports have associated obesity[2] and infertility.[21] with this type of cancer. As with breast cancer, nutritional-endocrine interrelations are probably important but factual data are lacking.

LIVER

Primary hepatic carcinoma is a major problem in certain population groups in many parts of the world.[20] It has been suggested that the high frequency of liver cancer in Africa is associated with coexisting cirrhosis and that a similar trend occurs elsewhere.[32] Although fatty liver is a common finding in protein-calorie malnutrition in children in areas in which primary liver cancer may be common, there is no good evidence to suggest a causal relationship. Various field studies have shown an association between liver cancer and the presence of aflatoxin in the food supply in African countries and in Thailand.[11, 12] There is as yet no direct evidence of a causal relationship although primary hepatoma occurred in a monkey after exposure to aflatoxin B_1 for six years.[1] The aflatoxin studies do not explain satisfactorily the preponderance of male victims; however, it is possible that males may convert aflatoxin to the ultimate carcinogen more efficiently than do females.

A factor which may be of major importance in the development of liver cancer is viral hepatitis, in as much as large segments of the population in Asia and Africa are infected with hepatitis B virus and the infection is contracted early in life, often at birth.[44] The relationship noted between this viral infection and primary hepatocellular carcinoma in Africa and Asia has now been observed in a European Caucasian (Greek) population with different racial, environmental, and dietary circumstances.[67] The interrelation of carcinogenic and viral factors is presently uncertain.

THE ROLE OF THE PHYSICIAN

It is apparent from this brief review that the data relating diet and cancer development are relatively scant and frequently contradictory, and that adduced associations are not proven etiologies. It is, therefore, difficult to give precise answers to a patient requesting advice on this subject. Any dietary advice must take into account economic, ethnic, and other acceptability factors. The advice should be part of an overall pattern designed to promote healthful and enjoyable living, and should include the following: (1) The use of tobacco products is to be avoided. (2) Ethanol is not contraindicated except in certain disease states, but it must be used in moderation (i.e., no more than the equivalent of 20 to 30 ml of ethanol per day). (3) Weight should be maintained within 5 to 10 per cent of "ideal" for height, sex, and age. (4) Regular exercise is desirable. (5) In view of the decreased mortality from coronary artery disease, the recommendations for a "prudent" diet should be continued with restriction of total fat (particularly saturated fat) with an increased proportion of polyunsaturated fat. Further investigation is necessary before a definitive statement can be made about a relationship between cancer and unsaturated fat. (6) Since total intake of meat has been related to an increased incidence of colon cancer, consideration should be given to restricting the amount of meat eaten. Precise figures on the amount of meat cannot be given with any assurance. (7) Whole grain cereals or other cereals with bran may play a role in minimizing colon cancer. In any case, better bowel regularity and decreased diverticulosis are benefits. (8) Foods containing nitrites and vegetables grown on soils high in nitrate, and water high in nitrate should be avoided. (9) Foods and beverages rich in ascorbic acid should be consumed regularly at all meals, not just at breakfast. The precise amount of ascorbic acid that is most likely to be beneficial is unknown, but "megavitamin" dosages are not indicated. (10) Regular consumption of charred foods should be avoided.

The physician is responsible for providing his patients with appropriate examinations at suitable intervals depending upon family history, presence of predisposing factors, and age. This should include chest and breast examinations, digital rectal examination, careful palpation of the prostate, pelvic examination and cervical smears, periodic sigmoidoscopy, and testing of stool for occult blood. These relatively

simple and inexpensive tests are still the most useful means of detecting cancer at a relatively early stage.

REFERENCES

1. Adamson, R. H., Correa, P., and Dalgard, D. W.: Occurrence of a primary liver carcinoma in a rhesus monkey fed aflatoxin B. J. Natl. Cancer Inst., *50*:549, 1973.
2. Armstrong, B., and Doll, R.: Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. Int. J. Cancer, *15*:617, 1975.
3. Berg, J. W.: Can nutrition explain the pattern of international epidemiology of hormone-dependent cancers? Cancer Res., *35*:3345, 1975.
4. Blot, W. J., Mason, T. J., Hoover, R., et al.: Cancer by county: etiologic implications. *In* Hiatt, H., Watson, J. D., and Winsten, J. A., eds.: Origins of Human Cancer. New York, Cold Spring Harbor Press, 1977.
5. Burkitt, D. P.: Epidemology of cancer of the colon and rectum. Cancer, *28*:3, 1971.
6. Burkitt, D. P., Walker, A. R. P., and Painter, N. S.: Effect of dietary fibre on stools and transit-times, and its role in the causation of disease. Lancet, *2*:1408, 1972.
7. Campbell, T. C., and Hayes, J. R.: Role of nutrition in the drug-metabolizing enzyme systems. Pharmacol. Rev., *26*:171, 1974.
8. Carrol, K. K.: Experimental evidence of dietary factors and hormone-dependent cancers. Cancer Res., *35*:3374, 1975.
9. Cohen, S. M., Wittenberg, J. F., and Bryan, G. T.: Effect of avitaminosis A and hypervitaminosis A on urinary bladder carcinogenicity of N-[4-(5-nitro-2-furyl)-2-thiazoly]formamide. Cancer Res., *36*:2334, 1976.
10. Conney, A. H.: Pharmacological implications of microsomal enzyme induction. Pharmacol. Rev., *19*:317, 1967.
11. Conney, A. H., and Burns, J. J.: Metabolic interactions among environmental chemicals and drugs. Science, *178*:576, 1972.
12. Copeland, E. M., MacFadyen, B. V., Jr., and Dudrick, S. J.: Effect of intravenous hyperalimentation on established delayed hypersensitivity in the cancer patient. Ann. Surg., *184*:60, 1976.
13. Correa, P., and Haenszel, W.: The epidemiology of large-bowel cancer. Adv. Cancer Res., *26*:1, 1978.
14. Cruse, J. P., Lewin, M. R., Ferulano, G. P., et al.: Carcinogenic effects of dietary cholesterol in experimental colon cancer. Nature, *276*:822, 1978.
15. Daly, J. M., Copeland, E. M., and Dudrick, S. J.: Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery, *84*:655, 1978.
16. Day, N. E.: Some aspects of the epidemiology of esophageal cancer. Cancer Res., *35*:3304, 1975.
17. Devesa, S. S., and Silverman, D. T.: Cancer incidence and mortality trends in the United States: 1935–1974. J. Natl. Cancer Inst., *60*:545, 1978.
18. de Waard, F., Cornelis, J. P., Aichi, K., et al.: Breast cancer incidence according to weight and height in two cities of the Netherlands and in Aiche prefecture, Japan. Cancer, *40*:1269, 1977.
19. Dickinson, L. E., McMahan, B., Cole, P., et al.: Estrogen profiles of Oriental and Caucasian women in Hawaii. New Engl. J. Med., *291*:1211, 1974.
20. Doll, Muir and Waterhouse, eds.: Cancer Incidence in Five Continents. New York, Springer, 1970.
21. Dunn, L. J., and Bradbury, J. T.: Endocrine factors in endometrial carcinoma. Amer. J. Med., *291*:1211, 1974.
22. Enig, M. G., Munn, R. J., and Keeney, M.: Dietary fat and cancer trends — a critique. Fed. Proc., *37*:2215, 1978.
23. Enstrom, J. E.: Colorectal cancer and consumption of beef and fat. Brit. J. Cancer, *32*:432, 1975.
24. Finegold, S. M., Sutter, V. L., Sugihara, P. T., et al.: Fecal microbial flora in Seventh Day Adventist populations and control subjects. Amer. J. Clin. Nutr., *30*:1781, 1977.
25. Gardner, L. I., and Amacher, P., eds: Endocrine Aspects of Malnutrition. Kroc. Fdn. Santa Ynez, California, 1973.
26. Glober, G. A., Kamiyama, S., Nomura, A., et al.: Bowel transit-times and stool weight in populations with different colon-cancer risks. Lancet, *2*:110, 1977.
27. Glober, G. A., Moore, J. O., Klein, K. L., et al.: Bowel transit-times in two populations experiencing similar colon-cancer risks. Lancet, *2*:80, 1974.

28. Goldberg, M. J., Smith, J. W., and Nichols, R. L.: Comparison of the fecal microflora of Seventh-Day Adventists with individuals consuming a general diet. Implications concerning colonic carcinoma. Ann. Surg., *186*:97, 1977.
29. Haenszel, W., Berg, J. W., Segi, M., et al.: Large-bowel cancer in Hawaiian Japanese. J. Natl. Cancer Inst., *51*:1765, 1973.
30. Harvey, R. F., Pomare, E. W., and Heaton, K. W.: Effects of increased dietary fibre on intestinal transit. Lancet, *1*:1278, 1973.
31. Hiatt, H., Watson, J. D., and Winsten, J. A.: Origins of Human Cancer. New York, Cold Spring Harbor Press, 1977.
32. Higginson, J.: The geographical pathology of liver disease in man. Gastroenterology, *57*:587, 1969.
33. Hill, M. J.: Colon cancer: a disease of fibre depletion or of dietary excess? Digestion, *11*:289, 1974.
34. Hill, M. J., Drasar, B. S., Williams, R. E. O., et al.: Faecal bile-acids and clostridia in patients with cancer of the large bowel. Lancet, *1*:535, 1975.
35. Hirayama, T.: Epidemiology of cancer of the stomach with special reference to its recent decrease in Japan. Cancer Res., *35*:3460, 1975.
36. Hoffman, F. L.: Cancer and Diet. Baltimore, Williams and Wilkins, 1937.
37. IARC Intestinal Microecology Group: Dietary fibre, transit-time, faecal bacteria, steroids and colon cancer in two Scandinavian populations. Lancet, 2:207, 1977.
38. Issenberg, P.: Nitrite, nitrosomines and cancer. Fed. Proc., *35*:1322, 1976.
39. Jasani, B., Donaldson, J., Ratcliffe, J. G., et al.: Mechanism of impaired glucose tolerance in patients with neoplasia. Brit. J. Cancer, *38*:287, 1978.
40. Jose, D. G., and Good, R. A.: Absence of enhancing antibody in cell-mediated immunity to tumor heterografts in protein deficient rats. Nature, *231*: 323, 1971.
41. Jose, D. G., and Good, R. A.: Quantitative effects of nutritional essential amino acid deficiency upon immune responses to tumors in mice. J. Exper. Med., *137*:1, 1973.
42. Larrson, L., Sandström, A., and Westling, P.: Relationship of Plummer-Vinson disease to cancer of the upper alimentary tract in Sweden. Cancer Res., *35*:3308, 1975.
43. Law, D. K., Dudrick, S. J., and Abdou, N. I.: The effects of protein calorie malnutrition on immune competence of the surgical patient. Surg. Gynec. Obstet.,*139*:257, 1974.
44. Linsell, C. H., and Peers, F. G.: Field studies in liver cell cancer. *In* Hyatt, Watson, and Winsten eds.: Origins of Human Cancer. New York, Cold Spring Harbor Press, 1977, pp. 549–556.
45. Lyon, J. L., and Sorenson, A. W.: Colon cancer in a low-risk population. Amer. J. Clin. Nutr., *31*:Suppl. 227, 1978.
46. Miller, E. C., and Miller, J. A.: Biochemical mechanisms of chemical carcinogenesis. *In* Busch, H., ed.: The Molecular Biology of Cancer. New York, Academic Press, 1974, pp. 377–402.
47. Mirvish, S. S., Cardesa, C., Wallcave, L., et al.: Induction of mouse lung adenomas by amines or ureas plus nitrite and by N-nitroso compounds: effects of ascorbate, gallic acid, thiocyanate and caffeine. J. Natl. Cancer Inst., *55*:633, 1975.
48. Mirvish, S. S., Wallcave, L., Eagen, M., et al.: Ascorbate-nitrite reaction: possible means of blocking the formation of carcinogenic N-Nitroso compounds. Science, *177*:65, 1972.
49. Nettesheim, P., and Williams, M. L.: The influence of vitamin A on the susceptibility of the rat lung to 3-methylcholanthrene. Int. J. Cancer, *17*:351, 1976.
50. Newberne, P.: Nitrite promotes lymphoma incidence in rats. Science, *204*:1079–1081, 1979.
51. Nutrition in the causation of cancer Symposium. Cancer Res., *35*:3235–3550, 1975.
52. Phillips, R. L.: Role of life-style and dietary habits in risk of cancer among Seventh-Day Adventists. Cancer Res., *35*:3513, 1975.
53. Pietsch, J. B., Meakins, J. L., and MacLean, L. D.: The delayed hypersensitivity response: application in clinical surgery. Surgery, *82*:349, 1977.
54. Reddy, B. S., Weisburger, J. H., and Wynder, E. L.: Effects of high risk and low risk diet for colon carcinogenesis or fecal microflora and steroids in man. J. Nutrition, *105*:878, 1975.
55. Reddy, B. S., and Wynder, E. L.: Large bowel carcinogenesis: fecal constituents of populations with disease incidence rates of colon cancer. J. Natl. Cancer Inst., *50*:1437, 1973.
56. Reddy, B. S., and Wynder, E. L.: Metabolic epidemiology of colon cancer. Fecal bile acids and neutral sterols in colon cancer patients and patients with adenomatous polyps. Cancer, *39*:2533, 1977.
57. Rogers, A. E., and Newberne, P. M.: Dietary effects on chemical carcinogenesis in animal models for colon and liver tumors. Cancer Res., *35*:3427, 1975.

58. Ross, M. H., and Bras, G.: Influence of protein under - and over - nutrition on spontaneous tumor prevalence in the rat. J. Nutr., *103*:944, 1973.
59. Ross, M. H., and Bras, G.: Tumor incidence patterns and nutrition in the rat. J. Nutr., *87*:245, 1965.
60. Rudell, W. S., Bone, E. S., and Walters, C. L.: Pathogenesis of gastric cancer in pernicious anemia. Lancet, *1*:521, 1978.
61. Shils, M. E.: Nutrition and neoplasia. *In* Modern Nutrition in Health and Disease. Philadelphia, Lea and Febiger, 6th ed., 1979.
62. Sporn, M. B., Dunlop, N. M., Newton, D. L., et al.: Prevention of chemical carcinogenesis by Vitamin A and its synthetic analogs (retinoids). Fed. Proc., 35:1332, 1976.
63. Stoerk, H. C., and Emerson, G. A.: Complete regression of lymphosarcoma implants following temporary induction of riboflavin deficiency in mice. Proc. Soc. Exp. Biol. Med., *70*:703, 1949.
64. Suskind, R. M., ed.: Malnutrition and the Immune Response. New York, Raven Press, 1977.
65. Tannenbaum, A.: Nutrition and cancer. *In* Hamberger, F., eds.: Physiopathology of Cancer. New York, Hoeber-Harper, 2nd ed., 1959, pp. 517–562.
66. Theuer, R. C.: Effect of essential amino acid restriction on the growth of female C57BL mice and their implated BW10Z32 adenocarcinomas. J. Nutr., *101*:223, 1971.
67. Trichopoulos, D., Tabor, E. Serety, R. J., et al.: Hepatitis B and primary hepatocellular carcinoma in a European population. Lancet, 2:1217, 1978.
68. Wattenberg, L. W.: Inhibition of carcinogenic and toxic effects of polycyclic hydrocarbons by phenolic antioxidants and ethoxyquin. J. Natl. Cancer Inst., 48:1425, 1972.
69. Wattenberg, L. W.: Inhibitors of chemical carcinogenesis. Adv. Cancer Res., *26*:197, 1978.
70. Weisburger, J. H., and Raineri, R.: Dietary factors and the etiology of gastric cancer. Cancer Res., *35*:3469, 1975.
71. White, J. W. Jr.: Relative significance of dietary sources of nitrate and nitrite. J. Agric. Food Chem., 23:886, 1975; 24:202, 1976.
72. Wogan, G. N.: Dietary factors and special psidemological situations of liver cancer in Thailand and Africa. Cancer Res., 35:3499, 1975.
73. Worthington, B. S., Syrotuck, J. A., and Ahmed, S. I.: Effects of essential amino acid deficiencies on syngeneic tumor immunity and carcinogenesis in mice. J. Nutr., *108*:1402, 1978.
74. Wynder, E. C.: The epidemiology of large bowel cancer. Cancer Res., 35:3388, 1975.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

Dietary Fiber

Bernard Levin, M.D., and David Horwitz, M.D.***

It has been recognized for many years that fiber affects bowel function. The observation that bread made from whole meal flour increased fecal output when compared to that made from sieved flour was made at the time of the Roman Empire.[5] Presently, physicians and members of the lay public are exposed almost daily to claims that an increased fiber intake may prevent or treat a wide variety of ailments ranging from diabetes to atherosclerosis to cancer of the large bowel. Most of these claims are based on "epidemiologic" data, but the observations comparing highly diverse populations make it difficult to identify and isolate causal differences from those of no consequence. To evaluate critically the evidence for the possible preventive or therapeutic benefits of fiber, it is important to consider current concepts of the physico-chemical nature of fiber and the complex modes by which fiber may influence gastrointestinal, endocrine, and lipid physiology. This review will focus on the influence of fiber intake on carbohydrate and lipid metabolism and the relationship of fiber intake to colon cancer.

Definition and Chemistry

A currently accepted definition of "dietary fiber" includes the skeletal remains of plant cells that are resistant to digestion by enzymes of man (Table 1). Hitherto, dietary fiber has been equated with crude fiber, a term used by animal nutritionists to define material isolated from animal foodstuffs by a single analytic technique which measures only a part of the true fiber content.[5] Terms such as residue, roughage, and bulk are imprecise and are of little value in furthering our understanding of fiber in the diet.

* Associate Professor of Medicine, University of Chicago, Chicago, Illinois
** Assistant Professor of Medicine, University of Illinois, Chicago, Illinois

Original studies described in this article were supported by USPHS grants AM 19206 and RR55. Dr. Horwitz is recipient of a USPHS Research Cancer Development Award (AM00181).

Table 1. *Components of Dietary Fiber*

PRINCIPAL DIETARY SOURCES	DESCRIPTION	NOMENCLATURE
Structural materials of the plant cell wall	Structural polysaccharides	Cellulose
		Hemicellulose
		Pectic substances
	Noncarbohydrate constituents	Lignin
		Minor components
Nonstructural materials either found naturally or used as food additives	Polysaccharides from a variety of sources	Pectin substances Mucilages Gums

Cellulose

Cellulose is the most widely distributed and only truly fibrous component of the cell wall. It is an unbranched 1,4-β-D-glucose polymer; these polymers are able to pack closely together, forming the cellulose fibers that are woven into the plant cell wall. Cellulose has the ability to take up water and swell, an action that is related to its ability to increase fecal weight.[45]

Hemicelluloses

Hemicelluloses in the plant cell wall consist of a wide variety of polysaccharide polymers. These polymers contain a mixture of pentose and hexose sugars. These substances consist of a "backbone" of xylose sugars with various sugar substitutions and degrees of branching. The presence in the compounds of uronic acids (e.g., galacturonic and glucuronic) which can behave as simple carboxylic acids and bind ions, may also be important in modifying luminal contents. These compounds may also have significant water holding capacity but the increase in fecal output following their ingestion also may be related to the metabolites (short chain fatty acids) rather than to water binding capacity.[8, 30]

Lignin

Lignin, a highly insoluble small polymer, is not a carbohydrate but a substituted phenylpropane. The cell is strengthened by the presence of lignin. Of possible significance in man is the property of lignin to absorb organic materials such as bile acids which may thus enhance the rate at which these materials are excreted in the feces.[10, 27]

Pectic Substances

Together with the hemicelluloses, the pectic substances form the matrix of the plant cell wall in which are enmeshed the cellulose

fibers. Unique to these compounds are the (1→4)-α-D-galacturonans occurring as such or as heteropolymers composed of other sugars as well.[6]

FIBER-ASSOCIATED SUBSTANCES

Phytic Acid

Phytic acid (inositol hexaphosphate) is ubiquitously found throughout the plant kingdom in association with protein. It is commonly complexed with calcium, magnesium, and potassium ions. In wheat, phytic acid is present in the aleurone layer of grain. During milling, this layer is removed. Phytic acid is not found in large amounts in white flour but is an important component of bran and wholemeal flour.[5] Phytic acid has the ability to bind calcium, magnesium, iron, and zinc which may be of significance in some populations in promoting deficiencies of these ions when dietary intake may be marginal.[38, 39]

Plant cell walls also contain a number of other substances which may have physiologic effects yet to be determined. These compounds include silica and lipids in the cuticular substances which cover the surfaces of fruits, leaves, and seeds. Also found are a variety of structural proteins, enzymes and non-metabolizable sugars such as raffinose which may promote the production of gas in man.[8, 15]

Fiber in the Diet

The overall fiber composition of the diet will obviously vary, depending on the foods that compose the diet. For example, using values for dietary fiber and not crude fiber, changes in the British diet over the past century have been assessed.[11] Since 1880, intake of dietary fiber had declined slowly except during World War II when it increased by 50 percent. This was attributable to changes in the milling of flours which resulted in an increase in the intake of non-cellulosic polysaccharides. The relative contribution of vegetables, fruits, and nuts to dietary fiber has increased slightly over the past century. It should be noted, too, that in wartime, fat consumption was reduced and this must be taken into consideration in assessing the impact of diet on health.

The structure and physiochemical characteristics of the components of dietary fiber will determine the part these polymers play in modifying luminal events. Of importance are solution viscosity of soluble polysaccharides, surface area and particle size of insoluble polysaccharides, ease and degree of hydration, crystallinity, density and ion-exchange properties.[28] In the plant, polysaccharide and lignin molecules intermesh, with specific resultant characteristics for that plant. These anatomic characteristics are altered or destroyed by chewing, digestion, cooking or processing. For example, excessive grinding of fiber causes hydrolysis of polysaccharides and delignification. Both factors may alter water-holding capacity[29] and other chemical properties.

Effects of Dietary Fiber on Carbohydrate Metabolism

Observations that diabetes, as well as ischemic heart disease, was rare in sub-Saharan rural African blacks, and that these populations ate a high carbohydrate, low fat diet containing a large fraction of cereal fiber, led to the "dietary-fiber hypothesis of the etiology of diabetes mellitus."[41] Trowell supported this hypothesis by pointing out that many of the diabetic syndromes occurring spontaneously in laboratory animals are seen in desert rodents which, in the wild, consume a diet of fibrous vegetation, but which are fed a diet of fiber-reduced laboratory chow in captivity. Similarly, African Bantus had lower glucose levels than South African whites, and rural South African blacks had a lower mean glucose level than urban blacks.[8] Although dietary fiber content was not specifically quantitated in any of these studies, the observations, and resulting hypothesis, stimulated a number of studies which further investigated this matter.

Kiehm et al.[25] studied 13 diabetic subjects given a diet which was high in both carbohydrate (75 percent of calories) and crude fiber (averaging 14.2 gm). The sources of dietary fiber were not stated. Five of these patients had been treated with sulfonylureas; the others were taking insulin. A significant fall in fasting plasma glucose levels was seen in all patients on sulfonylureas or less than 30 units of insulin a day. Insulin could be discontinued in four of the five patients who had required less than 30 units of insulin a day, and could be reduced in the fifth. However, no effect was seen in patients whose insulin requirement was over 30 units.[25]

To separate the effects of increased carbohydrate from those of increased fiber, Miranda and Horwitz studied eight insulin-dependent diabetic patients on two different diets, one of which contained 3 gm of crude fiber and the other 20 gm.[31] Calories and percentage of carbohydrate, fat, and protein were constant on both diets. The two diets were given, in random order, for 10 days each, and each patient's insulin dose was kept constant throughout the study. The source of dietary fiber varied from patient to patient, depending on food preferences, but in most patients was a commercially available high fiber bread in which the principle fiber is cellulose. Mean plasma glucose throughout the day was significantly ($p<0.001$) lower on the high fiber diet (120.8 ± 10.1 mg per dl) than on the low fiber diet (169.4 ± 11.7 mg per dl). Differences were found only in postprandial values, with fasting plasma glucose values similar on both diets (Fig. 1). Significantly more insulin reactions were seen in patients on the high fiber diets. Although this study did not establish the means by which high fiber diets lower plasma glucose, caloric malabsorption was unlikely as no patients had either a significant weight change or symptoms of malabsorption. Serum free insulin levels were the same on both diets, which was anticipated as insulin doses were not changed and none of the patients had endogenous insulin secretion. Interestingly, however, plasma glucagon levels were lower on the high fiber diet.

There are some interesting and unexplained differences between the above two studies. The Kiehm diet had more carbohydrate and less

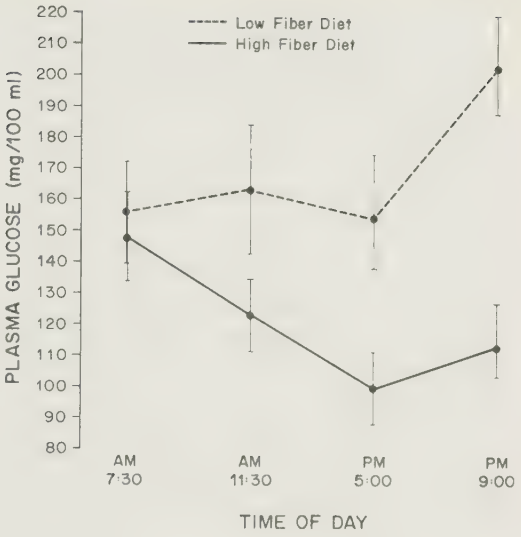


Figure 1. Mean (± SEM) plasma levels on high and low fiber diets. Modified from Miranda and Horwitz and reproduced with permission.

crude fiber than the Miranda study. While Kiehm et al.[25] found a fall in fasting plasma glucose levels in all subjects who responded to the diet change, Miranda and Horwitz found no change in mean fasting plasma glucose. In the Kiehm study only patients whose insulin dose was below 30 units responded, while Miranda found that the response did not depend on the insulin dose. Kiehm's patients were, on the average, 20 years older (48 ± 3 versus 28 + 4 yrs), but mean duration of diabetes was the same in both studies.

It is important to consider the type of dietary fiber in any study of carbohydrate metabolism. Jeffreys showed that glucose values significantly ($p<0.01$) reduced to less than 60 percent of control value at 60, 90, and 120 min if unprocessed bran (0.2 gm per kg of body weight) were given with the glucose.[15] On the other hand, if bagasse or wood cellulose were given with the glucose, *increases* of as much as 143 percent of control values ($p<0.01$) were seen in the blood glucose concentrations. Munoz et al. showed that glucose tolerance improved greatly in healthy subjects maintained 28 to 30 days on diets to which corn bran (92.1 percent fiber) and soy bean hulls (86.7 percent fiber) were added.[31] Hard red spring wheat bran (50.8 percent fiber) produced only moderate improvement, however, and soft white wheat bran (44.1 percent fiber) and textured vegetable protein produced no improvement.

Jenkins et al. examined the effects of adding guar flour (a storage polysaccharide) or pectin (a structural polysaccharide) to a test meal in both normal[21] and diabetic[20] subjects. Reductions in postprandial glucose levels were seen in all subjects, including three diabetic subjects taking 28 to 48 units of insulin daily. The normal and insulin-independent diabetics also showed lower insulin levels. The mechanism by which guar and pectin act is not known, but Jenkins et al.

have observed that if guar is hydrolyzed, so that it no longer forms a viscous solution, it no longer has an effect on postprandial glucose and insulin levels.[23] They have postulated that the viscous property of guar may be related to its effects on carbohydrate metabolism.

Haber et al.[13] have studied the effects of depletion or disruption of fiber by giving normal subjects test meals based on apples, in which intact apples were compared with the equivalent grams of available carbohydrate given as apple juice (fiber depleted) or apple puree (in which fiber is present but physically disrupted). They found similar rises in glucose after each meal, but greater hypoglycemic rebound after apple juice. Serum insulin rose most after juice, and least after intact apples. Although the juice could be consumed faster than the puree or apples, controlling this variable did not substantially alter the results. A subjective measure of satiety indicated that intact apples created the most satiety, and juice the least.

Monnier et al.[33] also studied differences between various types of indigestible fibers. Oral glucose (45 gm per sq. m) was given to chemical diabetics by itself, or combined with either pectin, cellulose, or cellulose phosphate. Pectin and cellulose phosphate produced the greatest reduction in peak glucose values, with cellulose causing a smaller reduction. All three substances reduced the rate of glucose rise, with pectin having the greatest effect and cellulose the least. In this study, none of the types of fiber had any effect on plasma immunoreactive insulin levels.

The above studies, while not a complete review of the literature, illustrate the range of findings regarding the effects of dietary fiber on carbohydrate metabolism, and particularly on diabetic control. It seems clear that fiber, or at least some types of it, can lower glucose levels both during glucose tolerance tests and after meals. While some studies show that the lower glucose levels are accompanied by lower insulin levels, others do not. It would appear, in any case, that the effects of dietary fiber on glucose levels are not insulin mediated. Although delayed absorption of glucose has been suggested, the precise mechanism by which fiber lowers blood glucose concentration remains unknown.

While all studies seem to agree on the glucose-lowering effect of guar and pectin, there is less agreement on other types of dietary fiber, particularly cellulose. For instance, as noted above, Jefferys noted an *increase* in glucose values when cellulose was added to a glucose tolerance test,[15] while Monnier et al.[33] found a *decrease*. The study of Miranda and Horwitz, which gave fiber predominantly as cellulose-containing bread, also noted decreased plasma glucose levels.[31] These contradictory findings probably indicate that not only the chemical composition of the fiber but its physical state, as well as its concentration and the manner in which it is mixed with the food, may be important.

It would be premature to draw conclusions on the appropriate role of dietary fiber in treating diabetes. While high fiber diets offer an attractive alternative to use of oral agents or insulin in adult-onset (non-

insulin-dependent) diabetic patients, it must be noted that their long-term safety and efficacy have not yet been proven. The longest reported studies have only treated patients for a mean of 15 months.[2] Concern has also developed that increased dietary fiber may lead to decreased absorption of calcium,[18, 37, 38] zinc,[18, 37, 38] magnesium,[18, 37] and phosphorus,[37] as well as ionized calcium.[35]

Should dietary fiber be increased for reasons other than treatment of diabetes, it should be remembered that diabetic control may change. In patients on insulin, the number of insulin reactions may increase.[31] In some patients, variation in day-to-day control may result from the use of the traditional diabetic diet "exchange lists," which allow free substitution of foods that are equivlaent in calories, carbohydrate, fat, and protein, regardless of fiber content. Until recently, detailed information on food content of dietary fiber has been difficult to obtain, although numerous tabulations of "crude" fiber are available. Recently, however, tables have been published making more complete information available.[1, 10] In some patients, more consistent intake of dietary fiber, at any fiber level, may help to stabilize diabetic control.

It should also be recalled that many patients may begin a high fiber diet without specific medical advice, as such diets are widely advocated in nonprofessional publications. This possibility should be considered when a change in the pattern of glucose control is seen in a diabetic patient.

The Role of Dietary Fiber in Regulating Serum Lipids

Cardiovascular disease, like diabetes, was first related to dietary fiber through epidemiologic studies.[6] For instance, Seventh Day Adventists, about half of whom follow a lacto-ovo-vegetarian diet, have a greatly reduced risk of coronary artery disease.[36] Numerous investigations have attempted to accurately define the effects of specific dietary fiber components on the various classes of serum lipids, and to determine the possible use of diets with modified fiber content in treating hyperlipidemic states.

Most studies have indicated that neither cellulose nor bran has any effect on serum cholesterol levels.[7, 26] Some of the human studies using bran have been criticized, however, because the bran had not been well defined chemically,[19] and because only normolipidemic subjects had been studied.[43] It remains possible that the effects of bran differ in hypercholesterolemic subjects. Furthermore, certain types of insoluble fiber have been shown to promote sterol excretion. For example, Story and Kritchevsky have shown that alfalfa binds an appreciable quantity of taurocholate, wheat straw, bran and oat hulls a smaller quantity, and cellulose and cellophane did not bind taurocholate.[42]

Soluble fibers, such as guar and pectin, appear to have a more definite effect on serum cholesterol levels. Jenkins et al.[22] found that mean serum cholesterol levels fell by 29.2 ± 9.5 mg per 100 ml after pectin (36 gm per day) was taken for 2 weeks, and by 36.3 ± 6.7 mg per

100 ml after adding 36 gm per day of guar gum to the diet. Thirty-six gm per day of wheat fiber, on the other hand, led to an insignificant rise (6.7±7.1 mg per 100 ml) in serum cholesterol.[22] Unfortunately, these amounts of guar and pectin may not be palatable to many patients, and so the place of such diets in treatment of hypercholesterolemia remains problematic.

The role of triglycerides in the pathogenesis of atherosclerosis is not as clear as that of cholesterol. It is generally felt to be desirable, however, to reduce abnormally high serum triglyceride levels. Heaton and Pomare[14] observed a small, but significant, fall in triglycerides from 118±57 (mean ±SD) to 100±53 mg per 100 ml when a mean of 38 gm per day of unprocessed wheat bran was added to the diet for 4 to 9 weeks.[14] Anderson and Ward, in their long-term (mean of 15 months) studies of diabetic subjects, found that mean triglyceride levels fell from 220±36 to 168±29 mg per 100 ml on a high-fiber, high carbohydrate diet, and fell further to 126±15 mg per 100 ml on a maintenance diet. Cholesterol levels, on the other hand, fell from 194±9 to 146±6 mg per 100 ml on the high-fiber, high-carbohydrate diet, but returned to 184±13 mg per 100 ml on the maintenance diet.[2]

Inadequate data are available to draw firm conclusions concerning the possible therapeutic use of modified fiber diets in treating lipid disorders or in lowering the risk of atherosclerosis. Although numerous animal studies have been done, the relevance of these studies to man is uncertain, both because of differences in metabolic functions and differences in "native" diets. Only a few studies have used chemically well defined types of fibers, and these studies, while easier to interpret, often give fiber in a form in which it does not naturally occur in foods. Finally, greater attention must be given to the effects of dietary fiber on specific classes of lipoproteins. For instance, it now seems clearly established that high density lipoprotein (HDL) cholesterol correlates inversely with risk of coronary artery disease, while low density lipopretein (LDL) cholesterol shows a direct relationship. Thus, it would be important in future studies to quantitate separately the effects of various types of dietary fiber on both HDL and LDL cholesterol.

Effects of Fiber on Colonic Function

STOOL WEIGHT. The rural African eats a diet high in fiber compared to those living in North America and Western Europe. As a result of this the rural African passes approximately 500 gm of stool per day compared to an individual who eats a low-fiber diet in whom an average daily stool weight is 100 gm per day.[6a, 32]

Bran has been used commonly in Western countries as an agent to relieve constipation and it has been shown that 16 gm of cereal bran per day produced softer and heavier stools. This increase in weight appears to be due to an increase in water content of the stool. Bran has the capability of absorbing up to three times its weight in water. Other compounds such as cellulose and hemicelluloses also are able to absorb water and this may explain in part the ability of fruits and vegetables, which contain these compounds, to increase stool weight. The actual constitu-

ents of the fibers responsible for water adsorption have not been defined. The water adsorbent moiety in the fiber has not been fully defined.

Transit Time. It has been shown that small bowel transit time is relatively constant in normal subjects, patients with constipation, and patients with diarrhea.[44a] Differences in gastrointestinal transit time are due, therefore, to changes in colonic transit. Using chromium sesquioxide as a marker for the solid phase of the stool and polyethylene glycol 4000 as a liquid phase marker, it has been shown that in normal patients, the solid and liquid phases will pass through the gastrointestinal tract at the same rate. In patients with ileal resection, the liquid phase travels faster than the solid phase and in diverticular disease patients, the solid phase travels faster than the liquid phase.[11a]

Dietary Fiber and Diverticular Disease

Painter and Burkitt have postulated that a fiber-deficient diet is responsible for the high incidence of diverticulosis in North America.[31a] They suggested that the "pressure" needed by the average Westerner to expel the stool was responsible compared to the effortless ease of the African who had a much softer stool. A number of studies have confirmed the benefits of a high fiber diet in patients with diverticular disease.[1a] This does not, of course, apply to the patient with acute diverticulitis.

Studies have indicated that bran shortens transit time in both normals and those with diverticular disease.[32] It alters also the fecal flow pattern and returned the pattern to a more normal state in which differential streaming of solid and liquid phases did not occur.

Irritable Bowel Syndrome

This common clinical disorder is applied to patients who have a variety of gastrointestinal symptoms that cannot be attributed to any recognizable pathologic process often after extensive clinical and radiologic evaluation. The symptoms include abdominal pain, flatulence, diarrhea and/or constipation, and hypersecretion of colonic mucus. A recent trial suggested that improvement in symptoms could be attained by using a combination of an antispasmodic drug, a mild tranquilizer, and a fecal bulking agent (ispaghula husk). A combination of two or three agents was better than any single agent. Bran was not used in this study and may be an equally effective and cheaper source of fiber.[38a]

COLON CANCER

Human Epidemiologic Studies

Studies of the geographic distribution of cancer of the large bowel, particularly its low incidence in Japan and other parts of Asia, sub-Saharan Africa (except among White South Africans) and most of South America (except Argentina), its increase among Japanese immigrants to Hawaii, and its high prevalence among North Americans, Western Europeans, and White South Africans, have fostered considerable speculation about the role of diet in the development of this neo-

plasm.[3, 9, 18] Burkitt has incriminated the typical Western diet which is low in fiber and causes fecal stasis.[5] This may lead to prolonged exposure of various compounds such as bile acids to the bacterial flora, which may metabolize these compounds and produce carcinogens. However, a direct correlation between colon cancer and dietary fiber is difficult to establish.[32] Other investigators have ascribed considerable significance to high intakes of fat and meat. Inhabitants of rural African communities with a low incidence eat a high fiber, low fat, low protein diet in contrast to high incidence countries where a low fiber, high protein, high fat diet is prevalent.

The relationships between dietary components may be complicated. The International Agency for Research on Cancer has investigated the possible dietary concomitants of the marked differences in rates of cancer of the colon and rectum noted in Denmark and Finland. Two areas were selected for detailed study of diet and stool bacterial count. These were a rural farming area of Finland and also Copenhagen with a prevalence of colorectal cancer approximately four times greater than the Finnish community. The dietary history of the population in Copenhagen was characterized by a higher intake of meat and beer, and a lower intake of fiber; a higher intake of fiber and milk was noted in Finland.[17] The effect of fecal lactobacilli on colonic luminal metabolism may be yet another factor which requires further investigation.

Fiber may exert its effect on the large bowel in other ways. For example, it has been demonstrated that North Americans on a general diet had a greater proportion of fecal coprostanol and coprostanone, which are bacterial metabolites of cholesterol, than did American vegetarians and Seventh Day Adventists.[48] Americans on the customary diet excreted more fecal bile acid than did the other groups. When acidic and neutral steriods are expressed as milligrams per kilogram of dry feces or of wet weight, changing to a diet with more unabsorbed fiber present, marketly affected these concentrations. When the diet was supplemented with 20 gm of bran per day, the stool weight increased, but the concentrations of fecal bile acids decreased.[11] If carcinogens are produced in the gut, perhaps partly related to high dietary fat intake, dilution of the colonic contents may be of therapeutic value. Various components of dietary fiber, such as lignin and pectin, can bind bile salts and alter their excretion, possibly preventing effects on the mucosa of the colon.

Other effects of increased fiber in the diet include decreased absorption of fat and nitrogen.[24]

Experimental Studies

Studies with experimental animals using carcinogens and modifications in dietary fiber have been conflicting. Using azoxymethane, Ward showed that the number of colonic neoplasms remained unchanged despite addition of cellulose in large quantities to a semisynthetic diet.[46] In a later study which utilized dimethylhydrazine, significantly reduced numbers of colonic neoplasms occurred in rats fed wheat bran, although the percentage of animals with invasive adeno-

carcinomas[47] was similar. Subsequently, Bauer and colleagues[11] investigated the effects of the addition of wheat bran, carrot fiber, and citrus pectin to a fiber-free diet after the administration of dimethylhydrazine. In the wheat bran and carrot fiber groups, the frequency of malignant colonic tumors was not significantly different from that of the group fed on the fiber-free basic diet. The rats fed on the diet with citrus pectin had an increased incidence of malignant colonic tumors. The reasons for this are unclear.

Freeman and Kim[12] have recently examined the effect of administration of dimethylhydrazine on colonic tumors in rats fed either a chemically defined fiber-free diet or a nutritionally and calorically equivalent diet containing a purified component, microcrystalline cellulose. Cellulose ingestion was associated with reduced numbers of animals affected by colonic tumors as well as a reduction in the total number of colon tumors in the animals.

The reasons for these differing results in experimental models remain to be elucidated.

CONCLUSION

It is obvious that the effects of fiber on colonic functions are complex. The typical "Western diet" which is high in fat and protein and low in fiber may alter the bacterial flora and milieu interieur of the gastrointestinal tract, particularly the colon, to produce a high incidence of colonic cancer. However, the exact nature of the interrelationships between these dietary constituents remains elusive and will undoubtedly be the subject of intense investigation in years to come.

ACKNOWLEDGMENTS

Thanks to Dr. Irwin Rosenberg for his encouragement and review of the manuscript and to Mrs. J. Gilpin for expert typing assistance.

REFERENCES

1. Anderson, J. W., Lin, W.-J., Ward, K.: Comparison of foods commonly used in diets for persons with diabetes. Diabetes Care, *1*:293–302, 1978.
2. Anderson, J. W., and Ward, K.: Long-term effects of high-carbohydrate, high-fiber diets on glucose and lipid metabolism: A preliminary report on patients with diabetes. Diabetes Care, *1*:77–87, 1978.
3. Armstrong, B., and Doll, R.: Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. Internat. J. Cancer, *15*:617–631, 1975.
4. Bauer, H. G., et al.: Effect of dietary fiber from various sources on the inducement of colonic tumors in the rat. Eur. Surg. Res., *10*(Suppl.):112–113, 1978.

4a. Brodribb, A. J. M.: Treatment of symptomatic diverticular disease with a high fibre diet. Lancet *1*:664–666, 1977.

5. Burkitt, D. P. Epidemiology of cancer of the colon and rectum. Cancer, 28:3–13, 1971.
6. Burkitt, D. P., Walker, A. R. P., and Painter, N. S.: Dietary fiber and disease. J.A.M.A., 229:1068–1074, 1974.

6a. Burkitt, D. P., Walker, A. R. P., and Painter, N. S.: Effect of dietary fiber on stools and transit times and its role in the causation of disease. Lancet, 2:1408–1411, 1972.

7. Connell, A. M., Smith, C. L., and Somsel, M.: Absence of effect of bran on blood lipids. Lancet, *1*:496–497, 1975.
8. Cummings, J. H.: What is fiber? *In* Spiller, G. A., and Amen, R. J., eds.: Fiber in Human Nutrition. New York, Plenum Press, 1976.
9. Doll, R.: The geographical distribution of cancer. Brit. J. Cancer, *23*:1–8, 1969.
10. Eastwood, M. A., and Hamilton, D. Studies on the absorption of bile salts to non-absorbed components of diet. Biochem. Biophys. Acta, *152*:165–169, 1968.
11. Findlay, J. M., et al.: Effect of unprocessed bran on colon function in normal subjects and in diverticular disease. Lancet, *1*:146–149, 1974.
11a. Findlay, J. M., Mitchell, W. D., Eastwood, M. A., et al.: Intestinal streaming patterns in cholerrholic enteropathy and diverticular disease. Gut, *15*:207–212, 1974.
12. Freeman, H. J., Spiller, G. A., and Kim, Y. S.: A double-blind study on the effect of purified cellulose dietary fiber on 1,2-dimethylhydrazine induced rat colonic neoplasia. Cancer Res., *38*:2912–2917, 1978.
13. Haber, G. B., Heaton, K. W., Murphy, D., et al.: Depletion and disruption of dietary fiber: Effects on satiety, plasma-glucose, and serum-insulin. Lancet, *2*:679–682, 1977.
14. Heaton, K. W., and Pomare, E. W.: Effect of bran on blood lipids and calcium. Lancet, *1*:49–50, 1974.
15. Hickey, C. A., Murphy, E. L., and Calloway, D. H.: Intestinal gas production following ingestion of commercial wheat cereals and milling factions. Cereal Chem., *49*:276–281, 1972.
16. Jefferys, D. B.: The effect of dietary fiber on the response to orally administered glucose. Proc. Nutr. Soc., *33*:11A–12A, 1974.
17. International Agency for Research on Cancer: Dietary fiber, transit time, fecal bacteria, steroids and colon cancer in two Scandinavian populations: Report from the International Agency for Research on Cancer Intestinal Microecology Group. Lancet, *2*:207–212, 1977.
18. Ismail-Beigi, F., Reinhold, J. G., Faradji, B., et al.: Effects of cellulose added to diets of low and high fiber content upon the metabolism of calcium, magnesium zinc and phosphorus by man. J. Nutr., *107*:510–518, 1977.
19. James, W. P. T., and Southgate, D. A. T.: Bran and blood lipids (letter). Lancet, *1*:800, 1975.
20. Jenkins, D. J. A., Goff, D. V., Leeds A. R., et al.: Unabsorbable carbohydrates and diabetes: Decreased post-prandial hyperglycemia. Lancet, *2*:172–174, 1976.
21. Jenkins, D. J. A., Leeds, A. R., Gassull, M. A., et al.: Decrease in postprandial insulin and glucose concentrations by guar and pectin. Ann. Intern. Med., *86*:20–23, 1977.
22. Jenkins, D. J. A., Leeds, A. R., Newton, C., et al.: Effect of pectin, guar gum, and wheat fiber on serum-cholesterol. Lancet, *1*:116–117, 1975.
23. Jenkins, D. J. A., Wolever, T. M. S., Haworth, R., et al.: Guar gum in diabetes. Lancet, *2*:1086–1087, 1976.
24. Kelsay J. L.: A review of research on effects of fiber intake on man. Amer. J. Clin. Nutr., *31*:142–159, 1978.
25. Kiehm, T. G., Anderson, J. W., and Ward, K.: Beneficial effects of a high carbohydrate, high fiber diet on hyperglycemic diabetic men. Amer. J. Clin. Nutr., *19*:895–899, 1976.
26. Kritchevsky, D.: Fiber, lipids and atherosclerosis. Amer. J. Clin. Nutr., *31*(Suppl.): S65–S74, 1978.
27. Kritchevsky, D., and Story, J. A.: In vitro binding of bile acids and bile salts. Amer. J. Clin. Nutr., *28*:305–306, 1975.
28. Lewis, B. A.: Physical and biological properties of structural and other nondigestible carbohydrates. Amer. J. Clin. Nutr., *31*:S82–S85, 1978.
29. McConnell, A. A., Eastwood, M. A., and Mitchell, W. D.: Physical characteristics of vegetable foodstuffs that could influence bowel function. J. Sci. Food. Agric., *25*:1457–1462, 1974.
30. McNeil, N. I., Cummings, J. H., and James, W. P. T.: Short chain fatty acid absorption by the human large intestine. Gut, *19*:819–822, 1978.
31. Miranda, P. A., and Horwitz, D. L.: High-fiber diets in the treatment of diabetes mellitus. Ann. Intern. Med., *88*:482–486, 1978.
32. Mitchell, W. D., and Eastwood, M. A.: Dietary fiber and colon function. *In* Spiller, G. A., and Amen, R. J., eds.: Fiber in Human Nutrition. New York, Plenum Press, 1976.
33. Monnier. L., Pham, T. C., Aguirre, L., et al.: Influence of indigestible fibers on glucose tolerance. Diabetes Care, *1*:83–88, 1978.
34. Munoz, J. M., Sanstead, H. H., and Jacob, R. A.: Improvement of oral glucose tolerance test and peripheral insulin activity by dietary fiber. Clin. Res., *26*:584A, 1978.
34a. Painter, N. S., and Burkitt, D. P.: Diverticular disease of the colon: A deficiency disease of Western civilization. Brit. Med. J., *2*:450–454, 1971.

35. Persson, I., Raby, K., Fonss-bech, P., et al.: Effect of prolonged bran administration on serum levels of cholesterol, ionized calcium and iron in the elderly. J. Amer. Geriatr. Soc., *24*:334–335, 1976.
36. Phillips, R. L., Lemon, F. R., Beeson, W. L., et al.: Coronary heart disease mortality among Seventh Day Adventists with differing dietary habits. A preliminary report. Amer. J. Clin. Nutr., *31*(Suppl.): S191–S198, 1978.
37. Reinhold, J. G., Faradji, B., Abadi, P., et al.: Decreased absorption of calcium, magnesium, zinc and phosphorus by humans due to an increased fiber and phosphorus consumption as wheat bread. J. Nutr., *108*:493–503, 1976.
38. Reinhold, J. G., Nasr, K., Lahimgarzadeh, A., et al.: Effect of purified phytate and phytate-rich bread upon metabolism of zinc, calcium, phosphorus and nitrogen in man. Lancet, *1*:283–288, 1973.
38a. Ritchie, J. A., and Truelove, S. C. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and isphaghula husk. Brit. Med. J., *1*:376–378, 1979.
39. Sanstead, H. H., et al.: Influence of dietary fiber on trace element balance. Amer. J. Clin. Nutr., *31*:5180—5184, 1978.
40. Southgate, D. A. T., Bailey, B., Collinson, E., et al.: A guide to calculating intakes of dietary fibre. J. Hum. Nutr., *30*:303–313, 1976.
41. Southgate, D. A. T., Bingham, S., and Robertson, J.: Dietary fiber in the British diet, Nature, *174*:51–52, 1978.
42. Story, J. A., and Kritchevsky, D.: Bile acid metabolism and fiber. Amer. J. Clin. Nutr., *31*(Suppl.):S199–S202, 1978.
43. Trowell, H.: Bran and blood lipids (letter). Lancet, *1*:801, 1975.
44. Trowell, H. C.: Dietary-fiber hypothesis of the etiology of diabetes mellitus. Diabetes, *24*:762–765, 1975.
44a. Waller, S.: Differential measurement of small and large bowel transit times in constipation and diarrhea: A new approach. Gut *16*:372–378, 1975.
45. Ward, K., and Seib, P. A.: Cellulose, lichenan and chitin. *In* Pigman, W., and Horton, D., eds.: The Carbohydrates. New York, Academic Press, 1970.
46. Ward, J. M., Yamamoto, R. S., Weisburger, J. H. Cellulose dietary bulk and azoxymethane-induced intestinal cancer. J. Natl. Cancer Inst. *51*:713–715, 1973.
47. Wilson, R. B., Hutcheson, D. P., and Wideman, L.: Dimethylhydrazine induced colon tumors in rats fed diets containing beef fat or corn oil with and without wheat bran. Amer. J. Clin. Nutr., *30*:176–181, 1977.
48. Wynder, E. L., and Reddy, B. S.: Epidemiology of cancer of the colon: Incidence, diet and metabolic factors. *In* Enker, W. E., ed.: Carcinoma of the Colon and Rectum, Chicago, Yearbook Medical Publishers, 1978.

Department of Medicine
University of Chicago
School of Medicine
Chicago, Illinois 60637

Trace Elements in Human Nutrition

Robert E. Burch, M.D. and Henry K. J. Hahn, Ph.D.***

Our understanding of the importance of the trace elements in human nutrition has received little practical consideration until recently. The occurrence of dietary deficiencies of trace elements was thought to be impossible because of the widespread distribution of trace elements in the environment. People are now beginning to appreciate the fact that such specific nutritional deficiencies do occur in human beings. These deficiencies can be detrimental to health as well as to growth and development.[5, 6, 51] Thus, trace element deficiencies in experimental animals, long known to veterinarians and nutritionists, have counterparts in human beings. Indeed, as in experimental animals, infants and young children seem to be more susceptible to the development of trace element deficiency states.

In general, trace element deficiencies can result from inadequate dietary intake (generalized malnutrition), impaired intestinal absorption, excessive excretion, certain disease states, as well as in patients maintained on prolonged parenteral nutrition without trace element supplements.

Although total parenteral nutrition solutions are formulated to provide nearly ideal nutrition, they lack a few essential nutrients, namely trace elements, essential fatty acids, and adequate amounts of vitamin E.[18] This is alarming in view of the fact that total parenteral nutrition is being used for longer periods of time with increasing frequency in the management of patients with gastrointestinal disease.[21]

Copper and zinc deficiencies have recently been reported in some patients who were on long-term total parenteral nutrition. Karpel and Peden[26] reported copper deficiency in one infant after long-term administration of total parenteral nutrition. The same phenomenon was observed and subsequently confirmed as copper deficiency in one adoles-

* Chief, Medical Service, Huntington VA Medical Center; Professor and Associate Chairman, Department of Medicine, Marshall University School of Medicine, Huntington, West Virginia

** Research Chemist, Huntington VA Medical Center; Assistant Professor, Department of Biochemistry, Marshall University School of Medicine, Huntington, West Virginia

This work was supported by the Veterans Administration and by a grant from the National Institute of Aging (5-R01-AG 01003).

cent and one adult with short bowel syndromes.[15] Both developed hypocupremia, neutropenia, and anemia following total parenteral nutrition and were successfully treated with copper supplements. Copper deficiency in an adult patient with systemic sclerosis treated with total parenteral nutrition has also been reported.[54] Skeletal changes associated with copper deficiency in infants receiving prolonged total parenteral nutrition has been shown to occur.[22] The skeletal changes in experimental animals are a specific effect of the copper deficiency unrelated to the concurrent anemia.[51] There is normal growth of cartilage with a marked failure of bone deposition in the cartilaginous matrix. Copper deficiency is rare in man but it has been documented in malnourished infants with chronic intestinal malabsorption.[10] It seems that infants and adults receiving prolonged total parenteral nutrition therapy are most susceptible to the development of copper deficiency. The reliable indicators of copper deficiency appear to be leukopenia and neutropenia, whereas the degree of anemia varies greatly from patient to patient. Many of these signs are identical to those caused by copper deficiency in experimental animals.[5, 51] One should remember that the nature of the anemia of copper deficiency is hypochromic and microcytic, and it is indistinguishable morphologically from that of iron deficiency. Malabsorption of iron was shown to occur in copper deficient swine and they subsequently developed microcytic hypochromic anemia.[49]

In experimental animals, copper deficiency produces a variety of striking pathologic abnormalities,[5, 51] including anemia, growth retardation, imperfect keratinization and pigmentation of the hair or wool, bone disorders, impaired reproductive performance, and skeletal deformities. Impaired pigmentation and keratinization of wool of sheep are the first signs to appear as a result of a lower copper level. Neonatal ataxia has never been reported in copper-deficient rats, pigs, or dogs, although it is a common finding in other mammalian species.

Zinc deficiency following total parenteral nutrition has also been reported. Kay et al.[27] described the classical features of swine parakeratosis with diarrhea, moist eczematoid dermatitis, particularly severe in the periorificial regions, and marked alopecia following total parenteral nutrition therapy. Plasma copper levels had also fallen far below normal in these adult patients but deficiency was not apparent.[27] Messing et al.[34] observed similar findings with increased hair loss and mental disturbances. Most of the symptoms were rapidly cleared by zinc therapy.

More severe zinc deficiency has occurred in children[3] and adults[50] receiving total parenteral nutrition without zinc supplements. The conditions were similar to acrodermatitis enteropathica including diarrhea, depression, alopecia, anal, and orificial skin lesions. Acrodermatitis enteropathica is an inherited disease. It is now recognized as a severe deficiency state.[35, 37] This deficiency seems to be a result of an inherited defect in zinc absorption. One important characteristic of this disease is susceptibility to infection. This is by far the most severe human zinc deficiency yet to be identified; however, it is reversible by oral zinc therapy. It is essential to treat these patients in early child-

hood with a sufficient dose of zinc to overcome the deficiency.[19] Hambidge et al.[32] reviewed the outcome of pregnancies in patients with acrodermatitis enteropathica who had survived without zinc therapy. The infants of these women had congenital malformations of the skeletal and central nervous systems. These are common findings in the offspring of zinc-deficient animals.[5, 51]

Zinc deficiency in human beings is one of the earliest studied subjects in trace element metabolism. Prasad et al.[41] described a group of 18 to 20 year-old Iranian males with iron deficiency anemia, hepatosplenomegaly, geophagia, hypogonadism, and dwarfism. The authors suggested that zinc deficiency was the cause of this syndrome. Similar findings were also observed in young Egyptian males.[42] Other abnormalities associated with zinc deficiency have been described and include impairment of wound healing and decreased acuity of taste and smell. Anorexia is frequently seen in conjunction with the aberrations of taste and smell. Although not proven in human beings, zinc deficiency during gestation in a number of animal species has teratogenic effects in the offspring. Similarly, zinc deficiency in animals is associated with impaired drug metabolism and decreased activity of the urea cycle enzyme ornithine transcarbamylase. However, neither phenomenon has yet been shown in humans.

The problem of trace element deficiencies should be a special concern to the pediatrician as a result of findings in the Denver Head Start Program.[20] Preschool children who participated in this program had a high incidence of biochemical indices of impaired zinc nutrition. Their growth was subnormal as were plasma and hair zinc concentrations. These children were from low-income families and their diets were high in refined carbohydrates which are poor sources of zinc. Even children from middle and upper-income families in the Denver area had a significant amount of poor zinc nutrition associated with poor growth, appetite, and impaired taste acuity. When zinc (2 mg per/kg of body weight) was supplemented, growth, appetite, and taste acuity became normal.[21]. The trace element deficiencies are most critical during prenatal and postnatal development because the trace element requirements are relatively high. Thus the children are more susceptible to such deficiencies. This is amply demonstrated in experimental animals.[5, 51] The premature infant is also at high risk from copper and iron deficiencies because the fetus lacks the ability to store these elements.

Formulas for the preparation of parenteral solutions of trace elements have been reported.[14, 32, 48] Dietary allowances of trace elements per day have been recommended by the Food and Nutrition Board, National Research Council, and the National Academy of Science (1974). Also there is a recommendation for intraveneous administration of trace elements by the American Medical Association.[57] Most of these preparations are concentrated with copper, manganese, zinc, iron, chromium, and iodine, but other trace elements are lacking. This could bring unforeseen future consequences in long term administration. The dose of trace element requirements varies with the rate of

growth and age of infants, during pregnancy and lactation, and in diseased states.

During TPN, periodic monitoring of plasma trace element concentrations is essential so that the dosage may be adjusted to prevent the development of any deficiency. Different trace elements may interact when several are administered at the same time. High-dose zinc therapy could induce copper deficiency if therapy is prolonged for more than a few months.[52] The mutual interactions occurring in biologic systems between copper, zinc, and cadmium have been demonstrated in chicks.[25] It is known that the elements whose physical and chemical properties are similar will act antagonistically to each other. Thus nutritional interactions between arsenic and selenium, manganese and iron, sulfur and selenium, and copper and iron are also a possibility. We have shown such interactions in zinc-deficient pigs.[7] The manganese and selenium concentrations of zinc-deficient liver were markedly reduced, whereas copper content was increased. Our study demonstrated that zinc deficiency is associated with tissue abnormalities of various trace elements other than zinc.

Bioavailability of trace elements in food varies considerably according to different dietary sources. Chemical forms of most trace elements in food are still unknown in spite of numerous analyses of the content of trace elements in food. Because of differences in bioavailability, information about the levels in food alone is insufficient to calculate the dietary requirement. For example, phytic acid interferes with the absorption of iron, zinc and others. Thus, diets high in phytic acid (unrefined cereals) will lead to negative balances of trace elements. Also trace element concentrations are low in refined high carbohydrate diets.

Hurley and her co-workers[16] showed that human milk contained a low-molecular-weight zinc-binding ligand (ZBL), but cow's milk did not. It has been suggested that zinc-binding ligand acts by enhancing the intestinal absorption of zinc in acrodermatitis enteropathica. Thus, it is the factor responsible for the therapeutic value of human milk in the treatment of a genetic disorder of zinc metabolism, acrodermatitis enteropathica.[16, 17] If the infants with acrodermatitis enteropathica are not maintained on human milk or supplemented with oral zinc, death will result within a few years.[35] The manifestations of acrodermatitis enteropathica occurred after the affected children were weaned from breast milk to formula or cow's milk.[4, 46] Thus human breast milk was thought to be an essential cure for acrodermatitis enteropathica.[38] Recent analysis of zinc content in various milks[25] demonstrated that cow's milk contains as much or more zinc than human breast milk. However, the bioavailability of zinc from human milk is consistently higher than that of most other milk.[25] Thus zinc-binding ligand in human milk seems to be a factor which is important in the poor absorption which occurs in acrodermatitis enteropathica. However, recent evidence indicates that bovine milk also contains low-molecular-weight zinc-binding ligand.[40] It is obvious that the role of zinc-binding ligand in neonatal nutrition has to be reevaluated.

GENETIC METABOLIC DISORDERS OF TRACE ELEMENTS

Two inherited diseases are related to abnormal copper metabolism, Wilson's disease and Menkes' kinky hair syndrome. Wilson's disease (hepatolenticular degeneration) is a well-recognized clinical entity characterized by a familial tendency, incoordination, ataxia, progressive mental deterioration, and a post-necrotic hepatic cirrhosis.[55] Patients with Wilson's disease show decreased plasma concentrations of copper and of ceruloplasmin. The relative amounts of copper bound by amino acids and albumin are increased. The rate at which blood is cleared of injected copper by all organs is depressed. Thus, hepatic uptake of copper is decreased and hepatic synthesis of ceruloplasmin is diminished. Despite diminished copper uptake, tissue copper content is generally increased. The high concentrations of copper in liver and brain are of particular importance to the pathologic dysfunction displayed by these organs. Urinary copper excretion is increased but excretion of copper via the biliary tract is markedly diminished; hence, fecal copper excretion is decreased.

The pathogenesis of Wilson's disease is unknown. Several investigators have produced considerable evidence that diminished excretion of copper through the biliary tract is the most significant physiologic aberration involved in copper retention.[8, 18] Other hypotheses have been: (a) increased absorption, based on higher levels of radioactivity in the blood after oral administration of radioactive copper, (b) increased binding of copper to hepatic protein, and (c) failure to form cerulopasmin. Although a diminished plasma ceruloplasmin concentration is a hallmark of the disease, it is not the only factor in the pathogenesis of Wilson's disease.

Treatment of Wilson's disease has broadly been directed toward removal of excess body stores of copper. Chelating agents, first BAL (2,3-dimercaptopropanol) and later penicillamine, have been helpful in increasing the urinary excretion of copper. Limitation of copper in the diet and addition of potassium sulfide, which diminishes copper absorption, have also proved helpful. Even with these measures, maintaining a negative copper balance may be difficult. Early diagnosis and persistent vigorous therapy will usually be rewarded by amelioration of symptoms or cessation in the progression of the disease.

The second inherited disease of copper metabolism is Menkes' kinky hair syndrome.[33] This disease is characterized by a progressive brain disease leading to death within the first year of life. The disease is also called "kinky" or "steel hair syndrome," because of an accompanying hair abnormality. This encephalopathy clinically appeared to involve most of the central nervous system, was accompanied by pili torti, and showed X-linked recessive inheritance. Scattered case reports have added the additional findings of abnormalities of the metaphyses of long bone, abnormal elastic tissue in arteries, and tortuosity of cerebral vessels. Danks et al.[11] reported seven cases and added hypothermia to the clinical picture described above. These investigators also found serum copper and ceruloplasmin to be subnormal in

the patients. It was shown that a marked accumulation of copper in the intestinal mucosa of these patients despite low plasma copper concentrations resulted from a net malabsorption of copper.[12] As in other defects, enteral and parenteral copper therapy has been applied to raise the plasma copper and ceruloplasmin level but there was no sustained improvement.

Acrodermatitis enteropathica has been described in a previous section. As stated, this disease is a rare inherited disorder. The pathogenesis of acrodermatitis enteropathica is now recognized to be attributable to an inherited defect in zinc metabolism.[35] The treatment of acrodermatitis enteropathica with oral zinc sulfate resulted in healing of the skin lesions as well as a rapid rise in the serum level of zinc. No toxic reactions have been reported using high oral zinc supplementation, except for occasional gastric distress in certain patients. Before the recent advent of zinc therapy, halogenated derivatives of the 8-hydroxyquinolines had provided effective therapy but this drug was only associated with a modest increase in plasma zinc concentration and urinary zinc excretion rates. Thus, acrodermatitis enteropathica seems to be a real zinc deficiency syndrome of human beings, the exact nature of which remains to be elucidated.

SECONDARY IMBALANCES IN TRACE ELEMENTS

A number of diseases have been shown to be associated with diminished levels of trace elements but specific trace element deficiencies have not been observed. Recently, Lombeck et al.[30, 31] have reported that dietetically treated patients with inborn errors of metabolism have lower serum selenium concentrations. The serum selenium levels of 32 patients with phenylketonuria, 3 patients with classic maple syrup urine disease, and one patient with a variant of maple syrup urine disease were markedly decreased in comparison to those of healthy children of a similar age group. Hair selenium concentrations were also lower than normal values. In addition, these same investigators[30, 31] have shown that the glutathione peroxidase activity of erythrocytes (selenoenzyme) in their patients was also decreased to 50 per cent of the normal values. Similar studies in England by Alexander et al.[2] demonstrated an imbalance of manganese and zinc in patients with phenylketonuria and maple syrup urine disease.

Schroeder and Nason[46] have conducted extensive analyses of trace elements on various pathological tissues and found a positive correlation between certain diseases and levels of trace elements. In kwashiorkor, combined deficiencies of zinc, copper, manganese, and chromium were observed. Another combined deficiency of zinc and manganese was present in chronic alcoholism. These investigators concluded that these trace elements could aid in the diagnosis of the diseases.

These studies clearly demonstrate that the trace element deficiencies or imbalances may play a fundamental role as secondary disturb-

ances in human trace element metabolism. However, the biological importance of these findings needs further clarification.

ROLE OF TRACE ELEMENTS IN AGING

It is universally accepted that the aging process occurs in all species. Nevertheless, a scientific description of what this process is or what is entailed in the process of aging is almost totally lacking. There are numerous theories but none of these can adequately explain aging. In fact, the results of many studies are conflicting and contradictory. One of the main reasons for conflicting results relates to faulty comparisons between young and old, growing and mature, or early and late maturation. Hence the validity of age comparisons from one study to another is doubtful. Systematic studies with more time increments are needed to clarify experiments utilizing age comparisons.

Enzymes assays and protein metabolism have been the most frequent focus of aging studies.[28, 36, 14] Unfortunately there has been little agreement on the experimental results, especially those concerning age-related enzyme patterns. A number of these enzymes are metalloenzymes and one of the major functions of trace elements relates to their incorporation into specific enzymes as integral components of a particular enzyme molecule. Zinc, among other trace elements, stabilizes the structures of RNA and DNA and it plays an important role in nucleic acid synthesis.[53] Since protein metabolism in aging is of fundamental importance, trace elements could play an important role in aging.

The effect of age on protein concentration in various tissues is shown in Figure 1. It can be seen that the concentration at birth (one day) was fairly high, then decreased sharply to minimum values at 2 to 4 days of age before increasing to constant levels. In general, con-

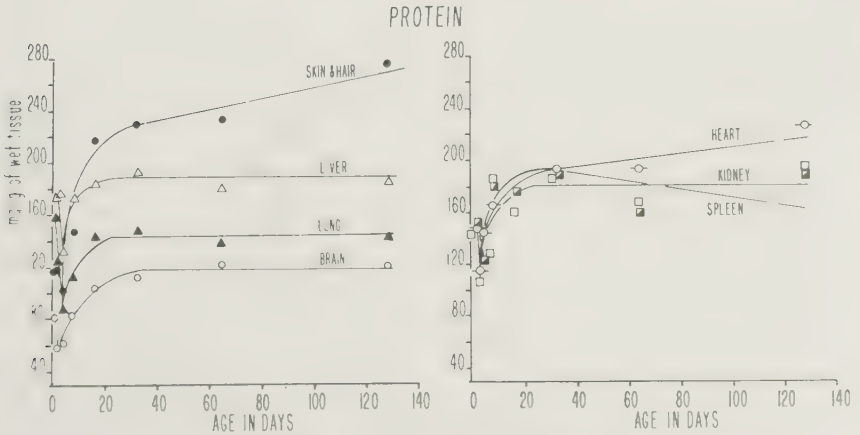


Figure 1. The effect of age on protein concentration in various tissues.

stant levels were reached at the weaning stage (21 days). Such an occurrence could be expected owing to the drastic physiologic changes that take place from maternal dependence in utero to self functioning at birth. Other studies[9, 43] have shown similar increases in protein content, but failed to observe the sharp decline postpartum.

At the present time very little information is available in the literature regarding tissue concentration of trace elements in relation to aging.[1, 13, 39] Linder and Munro[29] in reviewing the subject of iron and copper metabolism during development had to pool data from six different studies to develop a composite picture of hepatic copper content in rats from 5 days before birth to 90 days of age.

Figure 2 illustrates the selenium levels in different organs. In skin, hair, and brain selenium remained constant whereas kidney and lung selenium content continued to increase throughout the period of study after an initial increase and decline. Selenium content in the liver showed a gradual increase from birth. It is worthy to note that the selenium level in the kidney was consistently higher than the liver. It has been demonstrated that selenium functions as a component of glutathione peroxidase. The important role of selenium appears to be as a general protector of structural lipoproteins or of oxidizable lipid components of enzymes. The antioxidant activity appears to be clearly established as the primary function of this complex.

The effect of age on the manganese levels of different tissues is shown in Figure 3. The most fluctuation occurred in the weaning stage before leveling off. In contrast to other tissues, liver manganese increase from birth to 32 days of age. Subsequently the value remained fixed during the remainder of the test period. Manganese is a part of enzymes involved in urea formation, pyruvate metabolism, and the galactotransferase of connective tissue biosynthesis but the signifi-

Figure 2. The selenium levels in different rat organs.

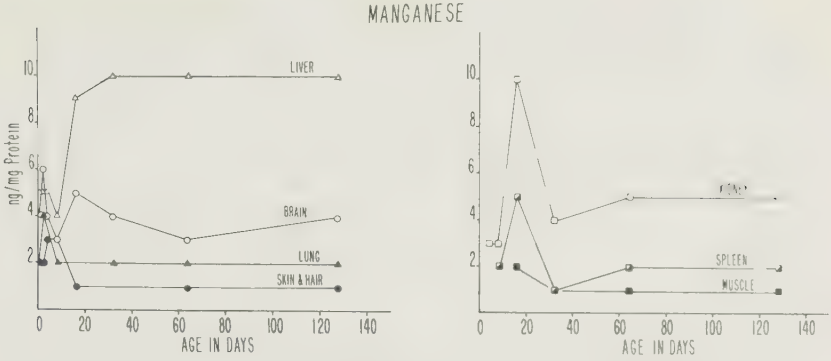


Figure 3. The effect of age on the manganese level in different tissues.

cance of increased manganese in liver is not known at the present time.

Other trace element concentrations in tissues fluctuated from birth to 32 days of age. This could be due to numerous factors. The most apparent explanation might be that the change in physiology at birth and variations in trace element content of the milk consumed could bring about such fluctuations. Trace element concentration of liver was very high at birth compared to adult levels. This could be the result of accumulation of trace elements in the fetal liver.[56] The results in our study showed zinc and copper content at birth were approximately four times that of adult levels whereas human fetal liver copper content has been reported to be ten times higher than adult liver content.[56]

In order to better understand the fluctuation of trace element concentration in suckling young, milk from lactating rats was analyzed for zinc and copper content. Both zinc and copper concentrations in milk decreased at 3 days than increased to maximum levels on the fourth day, followed by a rapid decline to a steady level on the thirteenth day. While the fluctuation between milk and tissue correlate, the concentration of zinc and copper in the milk is respectively 30 fold and 100 fold higher than in the highest tissue concentrations.

SUMMARY

Clinical recognition of the role of trace elements in human nutrition is increasing. Heretofore, many clinicians felt that the development of deficiency states was not likely except in very extreme conditions because the presence of trace elements in nature was so ubiquitous. The increased use of total parenteral nutrition seems to have made this viewpoint untenable. The recognition of additional genetic diseases of trace element metabolism such as Menkes' kinky hair syndrome and acrodermatitis enteropathica has also served to focus

clinical attention on trace elements. As time passes, no doubt, additional diseases of trace element metabolism will be recognized.

ACKNOWLEDGMENTS

We wish to thank Ms. Evelyn J. Schaffer for her valuable assistance during preparation of this manuscript.

REFERENCES

1. Abdulla, M., Jagerstad, M., Norden, A., et al.: Dietary intake of electrolytes and trace elements in the elderly. Nutr. Metab., *21* (Suppl. 1):41–44, 1977.
2. Alexander, F. W., Clayton, B. E., and Delves, H. T.: Mineral and trace-metal balances in children receiving normal and synthetic diets. Quart. J. Med., *43*:89–111, 1974.
3. Arakawa, T., Tamura, T., Igarashi, Y., et al.: Zinc deficiency in two infants during total parenteral alimentation for diarrhea. Amer. J. Clin. Nutr., *29*:197–204, 1976.
4. Barnes, P. M., and Moynihan, E. J.: Zinc deficiency in acrodermatitis enteropathica: multiple dietary intolerance treated with synthetic diet. Proc. Roy. Soc. Med., *66*:327–329, 1973.
5. Burch, R. E., Hahn, H. K. J., and Sullivan, J. F.: Newer aspects of the role of zinc, manganese and copper in human nutrition. Clin. Chem., *21*:501–520, 1975.
6. Burch, R. E., and Sullivan, J. F., eds.: Trace Elements. Med. Clin. N. Amer., *60*:653–849, 1976.
7. Burch, R. E., Williams, R. V., Hahn, H. K. J., et al.: Serum and Tissue enzyme activity and trace element content in response to zinc deficiency in the pig. Clin. Chem., *21*:568–577, 1975.
8. Cartwright, G. E., Markowitz, H., Shields, G. S., et al.: Studies on copper metabolism, XXIX. A critical analysis of serum copper and ceruloplasmin concentrations in normal subjects, patients with Wilson's disease and relatives of patients with Wilson's disease. Amer. J. Med., *28*:555–563, 1960.
9. Conde, R. D., and Scormik, O. A.: Faster synthesis and slower degradation of liver protein during developmental growth. Biochem. J., *166*:115–121, 1977.
10. Cordano, A., Placko, R. P., and Graham, C. G.: Brief report: hypocupremia and neutropenia in copper deficiency. Blood, *28*:280–283, 1965.
11. Danks, D. M., Campbell, P. E., Stereens, B. J., et al.: Menkes' kinky hair syndrome, an inherited defect in copper absorption with widespread effect. Pediatrics, *50*:188–201, 1972.
12. Danks, D. M., Stevens, B. J., Campbell, P. E., et al.: Menkes' kinky hair syndrome, Lancet, *1*:1100–1102, 1972.
13. Deeming, S. B., and Weber, C. W.: Hair analysis of trace minerals in human subjects as influenced by age, sex, and contraceptive drugs. Amer. J. Clin. Nutr., *31*:1175–1180, 1978.
14. Dudrik, S. J., and Rhoads, J. E.: New horizons for intravenous feeding. J.A.M.A., *215*:939–949, 1971.
15. Dunlap, W. M., James, J. C., and Hume, D. M.: Anemia and neutropenia caused by copper deficiency. Ann. Intern. Med., *80*:470–476, 1974.
16. Eckhert, C. D., Sloan, M. V., Duncan, J. R., et al.: Zinc binding: A difference between human and bovine milk. Science, *195*:789–790, 1977.
17. Evans, G. W., and Johnson, P. E.: Zinc-binding factor in acrodermatitis enteropathica. Lancet, 2:1310, 1976.
18. Fleming, C. R., Hodges, R. E., Smith, L. M., et al.: Essential fatty acid, copper, zinc and tocopherol deficiencies in total parenteral nutrition. Acta. Chim. Scand (Suppl.), *466*:20–21, 1976.
19. Hambidge, K. M.: Zinc and chromium in human nutrition. J. Human Nutr., 32:99–110, 1978.
20. Hambidge, K. M., Walravens, P. A., Brown, R. M., et. al.: Zinc nutrition of preschool children in the Denver Head Start Program. Amer. J. Clin. Nutr., *29*:734–738, 1976.
21. Hambidge, K. M., Hambidge, C., Jacobs, M., et al.: Low levels of zinc in hair, anorexia, poor growth and hypogeusia in children. Pediatr. Res., *6*:868–874, 1972.
22. Heller, R. M., Kirchner, S. G., O'Neill, J. A., et al.: Skeletal changes of copper deficiency in infants receiving prolonged total parenteral nutrition. J. Pediatr., *92*:947–949, 1978.

23. Hill, C. H., and Matrone, G.: Chemical parameters in the study of in vivo and in vitro interactions of transition element. Fed. Proc., *29*:1474–1481, 1970.
24. Jeejeebhoy, K. N., Zonhrob, W. J., Langer, B., et al.: Total parenteral nutrition at home for 23 months without complication, and with good rehabilitation. Gastroenterology, *64*:811–820, 1972.
25. Johnson, P. E., and Evans, G. W.: Relative zinc availability in human breast milk, infant formulas, and cow's milk. Amer. J. Clin. Nutr., *31*:416–421, 1978.
26. Karpel, J. T., and Peden, V. H.: Copper deficiency in long-term parenteral nutrition. J. Pediatr., *80*:32–36, 1972.
27. Kay, R. G., Tasman-Jones, C., Pybus, J., et al.: A syndrome of acute zinc deficiency during total parenteral alimentation in man. Ann. Surgery, *183*:331–340, 1976.
28. Klefenz, H. F., and Zuckerman, B. M.: Review: A comparative analysis of studies of enzyme changes with age with comments on possible sources of error. Age, *1*:60–67, 1978.
29. Linder, M. C., and Munro, H. N.: Iron and copper metabolism during development. Enzyme, *15*:111–138, 1973.
30. Lombeck, I., Kasperek, K., Harbisch, H. D., et al.: The selenium state of children II. Selenium content of serum, whole blood, Hair and the activity of erythrocyte glutathione peroxidase in dieteticially treated patients with phenylketonuria and maple-syrup-urine disease. Eur. J. Pediatr., *128*:213–223, 1978.
31. Lombeck, I., and Bremer, H. J.: Primary and secondary disturbances in trace element metabolism connected with genetic metabolic disorders. Nutr. Metab., *21*:49–64, 1977.
32. Matoi, J. R., and Jeffrey, C. P.: Formulation of a trace element solution for long-term parenteral nutrition. Amer. J. Hosp. Pharm., *35*:165–168, 1978.
33. Menkes, J. H., Alter, M., Steigleder, G. K., et al.: A sex-linked recessive disorder with retardation of growth, peculiar hair and focal cerebral and cerebellar degeneration. Pediatrics, *29*:764–779, 1962.
34. Messing, B., Pottras, P., and Bernier, J. J.: Zinc deficiency in total parenteral nutrition. Lancet, 2:97–98, 1977.
35. Moynahan, E. J.: Acrodermatitis enteropathica: A lethal inherited human zinc deficiency disorder. Lancet, 2:399–400, 1974.
36. Munro, J. N., and Young, V. R.: Protein metabolism in the elderly. Postgrad Med., *63*:143–149, 1978.
37. Neldner, K. H., and Hambidge, K. M.: Zinc therapy of acrodermatitis enteropathica. New Engl. J. Med., *292*:879–882, 1975.
38. Neldner, K. H., Hagler, L., Wise, W. R., et al.: Acrodermatitis enteropathica. A clinical and biochemical survey. Arch. Dermatol., *110*:711–721, 1974.
39. Persigehl, M., Schecha, H., Kasperek, K., et al.: Trace element concentration in human organs independent of age. Beitr. Path., *161*:209–220, 1977.
40. Piletz, J. E., and Ganschow, R. E.: Is acrodermatitis enteropathica related to the absence of zinc binding ligand in bovine milk? Amer. J. Clin. Nutr., *32*:275–281, 1979.
41. Prasad, A. S., Halsted, J. A., and Nadimi, M.: Syndrome of iron deficiency, dwarfism and geophagia. Amer. J. Med., *31*:532–546, 1961.
42. Prasad, S. S., Meale, A., Jr., Farid, Z., et al.: Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly dwarfism and hypogonadism. J. Lab. Clin. Med., *61*:537–549, 1963.
43. Rosso, P., Nelson, M., and Winick, M.: Changes in cellular RNA Content and alkaline ribonuclease activity in rat liver during development. Growth, *37*:143–151, 1973.
44. Rothstein, M.: Recent developments in the age-related alteration of enzymes: A review. Mech. Aging Develop., *6*:241–257, 1977.
45. Schroeder, H. A., and Nason, A. P.: Trace element analysis in clinical chemistry. Clin. Chem., *17*:461–474, 1971.
46. Schulze, R. R., and Winkelmann, R. K.: Acrodermatitis enteropathica: Report of a patient responding to combined therapy with human milk and diiodohydroxyquin. Mayo Clin. Proc., *41*:334–341, 1966.
47. Shils, M. E.: Guidelines for total parenteral solution. J.A.M.A., *220*, 1721–1729, 1972.
48. Sternlieb, I., Van den Hamer, C. J. A., Morell, A. G., et al.: Lysosomal defect of hepatic copper excretion in Wilson's disease (hepatolenticular degeneration). Gastroenterology, *64*:99–105, 1973.
49. Teague, H. S., and Carpenter, L. E.: Demonstration of a copper deficiency in young growing pigs. N. Nutr., *43*:389–399, 1951.
50. Tucker, S. B., Schroeter, A. L., Brown, B. W., et al. Acquired zinc deficiency. Cutaneous manifestation typical of acrofermatitis enteropathica. J.A.M.A., *235*:2399–2402, 1976.
51. Underwood, E. J.: Trace Elements in Human and Animal Nutrition, New York, Academic Press, 1971.

52. Underwood, E. J.: Trace element imbalances of interest to the dietitian. J. Amer. Dietet. Assoc., 72:177–179, 1978.
53. Vallee, R. L.: Zinc biochemistry in normal and neoplastic growth processes. Experientia, 33:600, 1977.
54. Vilter, R. W., Bozian, R. C., Hess, E. V., et al.: Manifestations of copper deficiency in a patient with systemic sclerosis on intravenous hyperalimentation. New Engl. J. Med., 291:188–191, 1974.
55. Walshe, J. M.: The physiology of copper in man and its relation to Wilson's disease. Brain, 90:149–176, 1967.
56. Widdowson, E. M., Chan, H., Harrison, G. E., et al.: Accumulation of Cu, Zn, Mn, Cr, and Co in the human liver before birth. Biol. Neonat., 20:360–367, 1972.
57. Guidelines for essential trace element preparations for parenteral use. J.A.M.A. (in press).

Marshall University School of Medicine
Huntington, West Virginia

Dietary Carbohydrates: Their Role in Cariogenicity

*Ernest Newbrun, D.M.D., Ph.D.**

The consensus that sugar consumption and caries are related is inescapable. It is based not only on epidemiologic surveys but on extensive animal experiments and controlled human studies. Bowen[10] has aptly stated: Evidence incriminating sugars has continued to accumulate from the results of epidemiologic and animal research and has now reached such proportions that no reasonable person would deny that frequent consumption of sugars by caries-susceptible humans will result in the development of dental caries. The report of a World Health Organization Scientific Group[92] on the etiology and prevention of dental caries concluded: Controlled human studies in man have established that the incidence and prevalence of caries can be markedly diminished by reducing the frequency of sugar consumption. There is convincing epidemiologic evidence that, in many large population groups, the prevalence of dental caries rises and falls with changes in total sugar consumption.

EXTENT OF THE PROBLEM

Dental caries, or tooth decay, continues to be a major public health problem. Untreated, caries can cause considerable pain and discomfort. The repair or replacement of carious teeth requires literally millions of hours per year and results in loss of time from school and industry. In 1969, the number of dental visits per person in the United States averaged 1.8 for children aged 5 to 14 and 1.7 for young adults aged 15 to 24. About 51 million hours of school time were lost that year by children having to visit the dentist. The cost of treating decayed teeth in the United States exceeds $2 billion annually, and there are approximately 1 billion unfilled cavities. To completely repair the nationwide damage due to caries would cost an additional $8 billion.[11]

*Professor of Oral Biology, Department of Oral Medicine and Hospital Dentistry, University of California, San Francisco, California

Table 1. *Prevalence of Caries in 5 Year Old Children and Mean def* Value in Carious Studies*

INVESTIGATOR	YEAR	PLACE	PER CENT WITH CARIES	MEAN DEF VALUE
Menczer	1956	U.S.A.	76.5	5.7
Wisan	1957	U.S.A.	74.0	3.5
Wells	1958	U.S.A.	86.0	6.0
Chung	1964	U.S.A.	66.0	3.5
Grey	1967	Canada	70.8	4.8
Stadt	1967	U.S.A.	74.2	4.1

*def = decayed, extracted, filled deciduous teeth.

Caries is the most prevalent affliction of childhood. At 3 years of age about 57 per cent of children have decayed teeth.[31] By the time they reach school age, more than 70 per cent of children have some tooth decay. The average 5 or 6 year old child has 5 decayed teeth, and by age 15 he or she has 10 decayed, missing, or filled teeth (Table 1). Recent United States Army surveys give a representative picture of the problem for young adults between the ages of 18 and 21. Every 100 inductees require 600 fillings, 112 extractions, 4 bridges, 21 crowns, 18 partial dentures, and 1 full denture.[11] Similar surveys of young Navy recruits reveal that the typical inductee requires about 5.4 restorations.[90] Thus, the prevalence of dental caries is exceedingly high and its economic impact on health care expenditure is considerable.

Young children are particularly vulnerable to decay for several reasons. First, newly erupted teeth are more susceptible to decay than teeth which have been in the mouth for some time.[12] Second, young children are less able to brush and floss their teeth adequately because they have not developed the necessary dexterity.[48, 85] Third, because they are growing rapidly and are highly active, young children are usually hungry not just at mealtimes but between meals, and will therefore eat and drink more than the customary three meals a day. Dental decay should not be lightly dismissed as just "holes in teeth," but should be recognized as potentially harmful to the child. Not only do decayed teeth spoil the child's appearance, but if left untreated they may cause pain and discomfort and interfere with a child's learning because of time lost from school. If decayed teeth are lost or extracted prematurely, orthodontic problems may also result.

DIETARY FACTORS AND THEORIES

Definitions

Dental caries is a pathologic process of localized destruction of tooth tissues by microorganisms.

The term "simple sugars" is used rather loosely by the public and often also by health professionals to include not only sucrose but other monosaccharides and disaccharides.[94] Sucrose (β-D-fructofuranosyl, α-D-glucopyranoside, cane or beet sugar) is the principal sugar consumed by man. Glucose (grape sugar) and fructose (fruit sugar) occur naturally in small amounts in fruits and vegetables and usually account for very little of the total sugar consumption. However, increasing amounts of glucose, maltose, and invert sugar (glucose and fructose in equal amounts) are being used in various processed foods.

Snack foods are those that are consumed other than at breakfast, lunch or dinner, need no preparation, and are ordinarily not eaten at table-type meals. In other words, there is nothing characteristic of snack foods other than in the manner and time of day of their use.

Etiology of Caries

Dental caries is a multifactorial disease in which there is an interplay of three principal factors: the host (particularly the saliva and teeth), the microflora, and the substrate, or diet. A fourth factor, time — which refers to the frequency of eating — must also be considered in any discussion of the etiology of caries.

The first step in the development of a carious lesion is the establishment of dental plaque, which is the soft, non-mineralized bacterial deposit forming on teeth that are not adequately cleaned. Not all plaques are cariogenic; some favor the development of periodontal disease. Those that are cariogenic have a typical bacterial composition dominated by organisms which ferment sugars as part of their metabolic processes. The fermentation of sugars produces acid. A cariogenic plaque is an acidogenic plaque, there being no doubt that acids are involved in the formation of caries. This so-called "chemoparasitic" theory of dental caries dates back to W. D. Miller[57] in 1890 and is supported by a great deal of experimental and clinical evidence collected in the intervening 80 years.

Every time food fermentable by the plaque microflora is ingested, acid is formed at the tooth surface and in the overlying dental plaque. This acid formation is reflected by a fall in pH or, conversely, by a rise in hydrogen ion concentration in the dental plaque. By inserting fine antimony electrodes into plaque on the smooth surface of anterior teeth, Stephan[81] showed that within 2 to 4 minutes of rinsing with glucose or sucrose solution, the pH fell from about 6.5 to about 5.0 and gradually returned to the original pH within 40 minutes. More recently, by using a biotelemetry device consisting of a miniature glass electrode (pH sensor) built into a removable appliance, it has become possible to obtain continuous and direct measurements of the pH of interproximal (between the teeth) plaque in situ at the tooth-plaque interface.[5, 9, 22, 36–39, 58] Another way of measuring plaque pH changes after ingestion of foods and beverages is to scrape off some plaque from tooth surfaces at various time intervals and place these plaques directly onto a pH electrode.[7, 15, 16, 19, 71]

All these methods have shown that after the ingestion of foods and

beverages containing sucrose and other monosaccharides and disaccharides, there is a rapid drop in plaque pH, which is sustained for various periods of time depending on the concentration of the fermentable sugar, the age and thickness of the plaque, and so forth. Many such exposures to acid are responsible for the development of a carious lesion.

The mineral phase (portion) of the tooth consists of hydroxyapatite crystals. At neutral pH, the saliva and plaque fluid are supersaturated with regard to plaque mineral (calcium and phosphate ions). As the pH falls, the equilibrium between the surrounding fluid and the mineral crystals is changed and mineral dissolution (demineralization) occurs. The lower the pH, the more the demineralization.

How fast a carious lesion forms will vary depending on the frequency of ingestion of fermentable sugars, the degree of oral hygiene, and so on. Early evidence of demineralization may be found after 3 weeks of rinsing the mouth 9 times a day with a sucrose solution and stopping all oral hygiene procedures.[17] Of course, caries usually takes longer to develop — about 18 ± 6 months.[67] In children with deciduous teeth, the thickness of enamel is less than that of permanent teeth, so that once a lesion is established it can penetrate the enamel and, if untreated, reach the pulp much more quickly than in older children, adolescents, or adults with permanent teeth. Once a cavity has formed, the process is irreversible and requires restoration. This demonstrates the obvious need for using preventive methods to reduce this widespread disease.

Types of Caries

Caries can be divided into several different types: pit and fissure caries, smooth surface caries, root caries, and deep dentinal caries. Pit and fissure caries are the most common type found in modern man, and form in sites where there are grooves or pits that trap food, so that bacteria can readily accumulate and are difficult to remove. Smooth surface caries occur between teeth and frequently along the gum line. Both of these types of decay begin in the enamel and have been linked to the ingestion of sugary foods and beverages. Root caries may occur in older individuals where the gums have receded and the roots are exposed. This type of decay has also been found in primitive populations and in ancient skulls.[74] The type of microflora associated with root caries is different from the predominant microflora found over pit and fissure and smooth surface lesions. Deep dentinal caries occur only after the enamel has already been destroyed, either beneath the pit and fissure or at a smooth surface site, and are associated with a predominance of lactobacilli in the lesion.

Cariogenicity of Sucrose

In discussing the role of diet in the caries process, two points should be emphasized: (1) Overwhelming evidence incriminates dietary sugar as the major factor in caries etiology. (2) This represents a consensus view and is by no means controversial.

The intimate cause-and-effect relationship between caries and the ingestion of sucrose has been well documented.[1, 41, 49, 51, 56, 60, 65, 75, 89] This relationship is based on a variety of observations including epidemiologic surveys linking caries prevalence to sucrose consumption, controlled human studies of institutionalized populations, and studies of persons with genetic defects that preclude sucrose from the diet. Innumerable laboratory tests on animals have also demonstrated the cariogenicity of sucrose in experimental diets.

Epidemiological Observations of Caries and Diet

Circumstantial evidence linking consumption of sucrose and prevalence of caries can readily be found in several epidemiologic surveys. The prevalence of caries among native populations such as Australian aborigines, New Zealand Maories, Eskimos, Ghanaians, and Tristan da Cunhans was very low before their exposure to European-type diets. The diets of these natives contained very little sucrose. Staple carbohydrate foods include cassavas, yams, maize, millet, and potatoes. As their diets changed to include more products containing sugar, caries prevalence increased.[62]

In England, which depends exclusively on imports for its supply of sucrose, records of the last 100 years show a steady increase in the per capita consumption of sucrose, from about 20 pounds per year in 1820 to over 100 pounds per year today. Present consumption of sucrose in the United States is about the same. This represents 15 to 20 per cent of an individual's caloric requirements. Concomitant with this increased consumption of sucrose has been an almost parallel rise in the prevalence of caries.[27] Conversely, surveys in Europe and Japan have demonstrated that caries were dramatically reduced during periods of wartime food restrictions when the consumption of sugar, syrup, and all sugar products was reduced.[78, 84, 86]

More recently, data from 19 countries have been compiled on sugar consumption and average numbers of decayed, missing, and filled (DMF) teeth of children 10 to 12 years old,[52] and are shown in Figure 1. These data reveal a very strong correlation between sugar consumption and dental caries experience. A similar trend of high prevalence of caries, or low percentage of persons free from caries, has been found among teenage South Africans with a high sugar intake. Conversely, rural Negroes of similar age eating less sugar had significantly less caries and more caries-free mouths.[69] This interpretation of the South African surveys is contrary to the conclusions of the authors but is supported by the overall data (see Fig. 2).

Controlled Human Studies

Vipeholm is a mental institution in southern Sweden. Adult patients on a nutritionally adequate diet were observed for several years and found to develop caries at a slow rate. Subsequently, the patients were divided into nine groups to compare the effectiveness of various changes in carbohydrate intake. Sucrose was included in the diet as toffee, chocolate, caramel, in bread, or in liquid form. Caries increased

Figure 1. Caries score (DMF-teeth) for children (11 to 12 years old) in 19 countries and corresponding annual per capita sugar consumption based on data of 1959. (Courtesy Prof. Dr. T. Marthaler.)

significantly when foods containing sucrose were ingested between meals. Not only the frequency but the form in which sucrose was ingested was important: sticky or adhesive forms of sucrose-containing foods, which can maintain high sugar levels in the mouth, were more cariogenic than those forms which were rapidly cleared.[26]

The Vipeholm study demonstrated that it was possible to increase the average consumption of sugar (from about 30 to 330 gm per day) with very little increase in caries (0.27 to 0.43 new carious surfaces per year), *provided* the additional sugar was consumed at meals in solutions. These observations in an institutional population, however, should not be misinterpreted to claim that the total amount of sugar consumed does not have an effect on dental caries, because the conditions were artificial. Where there is free choice and access to sugar-containing foods and beverages, such items are commonly eaten between meals. A survey by the Marketing Research Corporation of America[50] found that the total number of desserts served at meals de-

creased by 30 per cent in the period between 1962-1963 and 1967-1968. During the same time interval, servings of these dessert foods as snack items increased by 40 per cent. Snack foods now account for about 15 per cent of the average person's total caloric intake. This represents a substantial growth in the snack food area and, as a corollary, an increased risk of caries. In general, therefore, the more sugary foods and drinks consumed, the more decay. Undoubtedly, the minimal sucrose content required for cariogenicity will vary with the stickiness or oral clearance and the frequency of ingestion of that food item.

Hopewood House was an orphanage in Bowral, New South Wales, Australia, which at one time accommodated 82 children. From its very beginning, sugar and other refined carbohydrates were excluded from the children's diet. Carbohydrates were served in the form of wholemeal bread, soya beans, wheat germ, oats, rice, potatoes, and some treacle and molasses. Dairy products, fruit, raw vegetables, and nuts were prominently featured in the typical menu. Dental surveys of these children from the ages of 5 to 13 revealed an average def (decayed, extracted, filled deciduous teeth) and DMFT (decayed, missing, and filled permanent teeth) score of 1.1, which was about 10 per cent of the caries prevalence of the public school population in that age group. As the children grew older, they were relocated and no longer adhered to the original diet which had limited caries almost completely. The steep increase of DMFT in the children at about 13 years of age[28] corresponded to the deviation in dietary habits. This indicates that these teeth had not acquired any permanent resistance to caries. The reason the teeth had not decayed during the prepubertal period

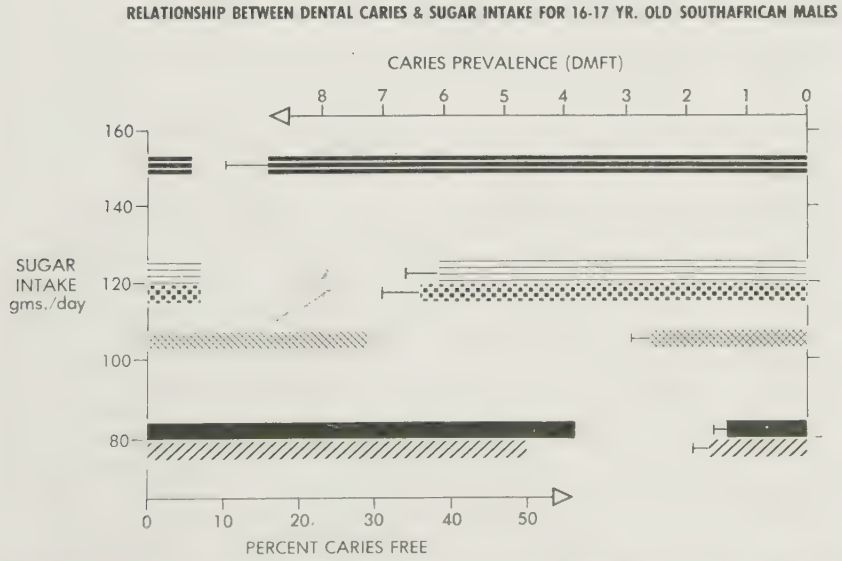


Figure 2. Relationship between dental caries and mean sugar intake (gm/day) for South African males (16 to 17 years old) of four different ethnic groups. There is a direct relationship between prevalence of caries (DMFT) and sugar intake and an indirect relationship between percent population caries-free and sugar intake. (Drawn from data of Retief et al.[60])

was that the oral environment was not conducive to decay because few, if any, cariogenic foods were ingested.

Hereditary fructose intolerance is an uncommon metabolic disorder caused by reduced activity of a liver enzyme, fructose-1-phosphate aldolase, normally involved in the metabolism of fructose. Persons with hereditary fructose intolerance develop nausea, vomiting, malaise, excessive sweating, tremor, coma, and/or convulsions after ingesting foods containing fructose. The most common source of fructose in the diet is foods containing sucrose, since sucrose is constituted of one molecule of glucose and one molecule of fructose. Persons with hereditary fructose intolerance have a strong aversion to all sweets, cakes, candies, and fruit. They eat glucose, galactose, lactose, and starch-containing foods such as milk, dairy products, bread, semolina and oat cereals, noodles, spaghetti, rice, and usually potatoes. These individuals are either caries-free or have very little decay.[53, 62] The low prevalence of caries in these patients indicates that starchy foods do not produce decay whereas sugary foods do.

Evidence from Animal Studies

Although the exact diet and the species of rodent tested have varied, the conclusions from innumerable animal studies are the same: a diet containing sucrose is markedly more cariogenic than a similar diet containing starches.

Rodents have been widely used — and often misused — for testing the cariogenicity of foods. Because the findings of such studies are sometimes inconsistent, rodent caries have been dismissed as having no significance for man.[6] However, if this animal model is tested under conditions in which such factors as the species, age, and preweaning regimen of the animal, the caries scoring system, the infecting microorganism, and the duration of the experimental period are standardized, a similar pattern of caries is found.[35, 47] Furthermore, foods can be tested individually, which is impossible in human clinical trials. Stephan[82] compared the cariogenicity of a wide range of foods and beverages fed to rats *ad libitum* in addition to their basic diet. Generally, items with a high sucrose and high total sugar content were highly cariogenic, and those with no or low sugar content (soda crackers, milk, sorbitol) were noncariogenic (Table 2). The correlation is not perfect, but the exceptions can be explained by the marked taste preferences of rats. For example, rats drink sweetened solutions (sucrose water, cola) very frequently if they are continuously available, which accounts for their relatively high caries score. Similarly, given the opportunity, rats eat apples with great frequency. Conversely, rats do not like chewing gum as much as human beings do, and probably the same holds true for caramels, so that these foods were not as cariogenic as would be expected from their sugar content. These experiments need to be repeated under controlled feeding conditions to eliminate the frequency and preference factors. When rats are fed less diverse types of foods, a close parallel is found between sucrose content and cariogenicity, particularly of smooth surface lesions (Table 3).[40] Hamsters fed various commercial cereals develop smooth surface

Table 2. *Comparison of Caries Score and Sucrose Content of Human Foods Fed to Rats* Ad Libitum*

FOOD	PER CENT SUCROSE†, Φ	PER CENT TOTAL SUGAR	CARIES SCORE
Sucrose	99.5	100	62.1
Milk chocolate	42	55	34.1
Dates	47	84	32.7
10 per cent sucrose water	10	10	32.3
Raisins	14	70	29.6
Cola	3	11	24.7
Candy mints (Lifesavers)	78	89	23.8
Chocolate sandwich cookie (Oreo)	35	35	21.0
Bananas	9	20	19.4
Apples	3	11	19.2
Honey graham crackers	16	18	16.0
Caramels	64	77	14.0
Chewing gum (Wrigley's)	55	59	10.3
Figs	0.1	73	0.3
Soda Crackers	0	<1	0
Milk	0	5	0
Sorbitol	0	0	

*Rats fed Diet 581 (non-cariogenic) for 1 hour twice a day. Test food was continuously available.

†Shannon (1977).

Φ Pennington (1976).

Table 3. *Cariogenicity of Snack Foods Fed to Rats* Ad Libitum*

FOOD	PER CENT SUCROSE	PER CENT SUGAR	CARIOUS FISSURE LESIONS	CARIOUS BUCCO-LINGUAL LESIONS
Milk chocolate and Rice Crispies	42	50	12.9	43
Chocolate wafers	30	35	11.2	30
Biscuit, whole meal flour	20	22	8.0	5
Biscuit, white flour	14	19	10.6	2
Bread and jam	7	15	3.0	1.5
Biscuit, "sucrose-free"	1	3	2.6	0
Bread and cheese	0.4	3	3.1	0

From Ishii, T., König, K. G., and Mühlemann, H. R.: Helv. Odontol. Acta., *12*:41, 1968.

Table 4. *Influence of Commercial Cereals on Dental Caries in Hamsters**

CEREAL	PER CENT SUCROSE†	CARIES SCORE
Frosted Flakes	44	17.14 ± 0.36
Cap'n Crunch	43.3	14.21 ± 0.24
King Vitaman	58.5	14.09 ± 0.27
Quisp	44.9	10.46 ± 0.15
Corn Flakes	7.8	8.95 ± 0.14
Corn Starch	0	8.46 ± 0.19
Cheerios	2.2	7.66 ± 0.12
Life	14.5	6.92 ± 0.12
Special K	4.4	6.85 ± 0.11
Shredded Wheat	1.0	6.07 ± 0.12

From McDonald, J. L., and Stookey, G. K.: J. Dent. Res., 56:1001, 1977.
†Constituted 33 per cent of total diet.

caries proportionate to the sucrose content of the cereal (Table 4).[54] Similarly, rats fed breakfast cereals containing 0, 9.5, or 45 per cent sucrose had caries scores of 5.3, 13.8, and 20.0 respectively.[23] One exception, Life cereal, has a relatively low cariogenicity, presumably because of its higher mineral and phosphate content.[54]

BIOCHEMICAL AND MICROBIOLOGIC EVIDENCE

The key role of sucrose as a dietary substrate in the caries process, particularly on smooth surfaces, can be explained on biochemical grounds. Smooth surface caries depends on the growth of dental plaque. Extracellular polysaccharides, both glucans and levans, have been demonstrated in plaque.[25, 61] The glucans, particularly the water insoluble fraction, can serve as structural components of the plaque matrix, in effect "gluing" certain bacteria to the teeth. Soluble levans and some of the soluble glucans are degradable by the plaque flora and may function as transient reserves of fermentable carbohydrates, thereby prolonging the production of acid. In the biosynthesis of these polysaccharides by bacterial enzymes, glucose units are transferred from sucrose to the active site and inserted between the enzyme and the reducing end of the polymer. The enzyme conserves the relatively high energy of the link between the two anomeric carbons, C1 of glucose and C2 of fructose, found in sucrose. Disaccharides other than sucrose, such as maltose and lactose, are hemiacetals, not dihemiacetals. Therefore their free energy of hydrolysis is significantly less and they cannot serve directly as glycosyl donors in the system. Sucrose, on the other hand, has a free energy of hydrolysis of −6600 calories per mole, which is in the same range as the nucleoside diphosphate sugars, −7600 calories per mole, and higher than glucose-1-phosphate. Because sucrose is unique in serving as a substrate not only for fer-

mentation but also for synthesis of extracellular polysaccharides, it influences the ecology of the oral microflora. It does this by favoring the colonization of the plaque by caries-inducing organisms such as *Streptococcus mutans*. This was first demonstrated in hamsters: when fed lab chow and infected with caries-inducing streptococci "labeled" by being made resistant to streptomycin, these animals had only a few of these organisms recoverable in their mouths after three weeks.[42, 43] On the other hand, recovery of these "labeled" streptococci from hamsters maintained on diets containing sucrose was consistently high. These studies have since been extended to humans, in whom it has been demonstrated that frequent chewing of sucrose favors the implantation of cariogenic streptococci in plaque.[11, 83] The frequency of isolation and the numbers of *Strep. mutans* found in the plaque from patients with hereditary fructose intolerance is far less than in their normal siblings who eat sugary foods.[32] The extracellular polysaccharides formed from sucrose facilitate the adherence of *Strep. mutans* to teeth; in the absence of sugar from the diet, fewer of these cariogenic bacteria can stick.

In summary, then, the unique biochemical properties of sucrose enable it to influence the oral ecology and favor the colonization in dental plaque of caries-producing microorganisms. In both human beings and animals, ingestion of sugar has been clearly demonstrated as the major dietary factor contributing to caries. The sugar content of food is obviously not the only factor affecting cariogenicity; the physical texture and especially the frequency of ingestion are also of importance. Nevertheless, labeling that discloses the percentage of sucrose in a food would be a useful guide to consumers and would help professionals giving dietary advice.

CONFLICTING OPINIONS

Representatives of the food industry have attempted to justify their high use of sugar by hiding behind such statements as "the scientific community cannot agree on what foods are cariogenic." A very small minority of nutritionists and dentists have described the relationship between sugar-containing foods and tooth decay as "controversial."[69, 87] There is no unanimity on the relationship between sugar-containing foods and tooth decay; however, unanimity on any issue is rare. Unquestionably there is a consensus that frequent intake of sugary foods promotes caries.[1, 29, 49, 56, 65, 75, 89]

A number of human clinical trials, particularly those in which only one sugar-containing item such as breakfast cereal,[21, 70] soft drink,[80] or candy[2] is the variable, have been interpreted as indicating that specific sugar-containing products are not cariogenic. However, the design of these studies suffers from infirmities. In such trials the intake of other sugar-containing foods is not controlled and, regrettably, is generally frequent and considerable. Consequently there is a high caries activity in the "normal" groups, i.e., a high background "noise" level

(Table 5). In the United States and some European countries, sugar consumption is well over 100 pounds per person per year.[66, 93] Slight variations in this amount are unlikely to cause a significant difference in caries increments. It is incorrect, therefore, to claim that there is "no association" between the consumption of presweetened cereals and the incidence of caries.[13, 30] Rather, a poorly controlled human model will not show statistical differences, whereas when the diet is well controlled and the caries increments in the sugar-restricted groups are small, significant differences are evident (Table 6). Hamsters, fed various commercial cereals which were the only source of sucrose, developed caries proportionate to the sucrose content of the cereal,[51, 63] as shown in Table 4. Between-meal chewing of sugary gum, 2 or 5 times a day, increases the rate of decay.[18, 20] In one clinical trial involving 6 to 12 year old children, those who chewed two sticks of sugar-containing gum a day between meals had 30 to 60 per cent more new DFS than a group of children who were not supplied with chewing gum (Table 5).

Cross-sectional surveys of populations in which investigators attempt to relate dietary habits, based upon a 24-hour recall, to prevalence of caries can be misleading — particularly so if one is examining an older population where the prevalence data measure the cumulative effect of dietary habits of many years.[3, 4, 45, 46] It is unreasonable to expect that one 24 hour or even a week's dietary survey can be related to an indeterminate time during which dietary habits can change. Clearly, longitudinal measurements of caries increments and repeated diet histories are essential to any study of the association between caries and eating. Furthermore, the data of Kreitzman[46] are based on total carbohydrate intake and measure neither the amount nor the fre-

Table 5. *Annual Increments of Caries in Subjects Eating "Normal" Diet and Sugar-Supplemented Diet*

DIET		AGE	AUTHORS
"Normal"	Sugar Supplement	YRS.	
Water 2×/day 3.42 DMFS	Sugar soft drink 2×/day 4.05 DMFS	8–21	Steinberg *et al.* 1972
Breakfast cereal non-eaters 2.14 DMFS	Breakfast cereal eaters (60% presweetened) 1.73 DMFS	13	Rowe *et al.* 1974
Regular breakfast cereal 1.92 DFS	Presweetened breakfast cereal 1.84 DFS	7–11	Glass and Fleisch 1974
Sugarless gum 5×/day 1.97 DMFS	Sugar gum 5×/day 2.37 DMFS	12.5	Finn and Jamison 1967
No gum 1.92 DFS	Sugar gum 2×/day 2.61 DFS	6–12	Glass 1978

Table 6. *Comparison of Annual Caries Increments of Subjects on Sugar-Restricted Diets with Subjects on Unrestricted Diets*

STUDY	DIET		PER CENT CARIES REDUCTION
	RESTRICTED	UNRESTRICTED	
Vipeholm*	Low sugar, none between meals 0.67 DMFS	24 toffees/day between meals 4.02 DMFS	83
Hopewood House†	Sugar restricted, vegetarian 0.88 DMFT	Unrestricted 1.81 DMFT	51
Turku‡	Sugar substituted by xylitol 0.74 DMFS	Sugar used as sweetener 1.67 DMFS	57

*Gustafsson *et al.* (1954). Patients about 31 years old.
†Harris (1963). Children 10–13 years old compared with public school children.
‡Scheinin (1978). Adults and children, average age 27.5.

quency of sucrose ingestion. Predictably there is no relationship between total carbohydrate intake and caries prevalence.

INDICATORS OF CARIOGENICITY

What do highly cariogenic foods have in common? Undoubtedly they are foods eaten frequently, often between meals; in other words, snack foods. They have the ability to lower the pH of plaque. They are adhesive or sticky and may be retained in the oral cavity for a long period of time. Finally, they invariably contain sucrose or some other fermentable sugar. The relationship between dietary sucrose content and caries may not be exactly linear. The curve may rise sharply and flatten out, so that increasing the sucrose content of the diet beyond a certain level does not increase caries[31] or cause any further pH drop in the plaque.[15] In animals, this flattening out of the curve may be explained by the fact that once the threshhold level of sucrose in the diet is reached, almost all the susceptible surfaces at risk are already affected. Conversely, until the percentage of sucrose in the diet is decreased below a certain level, there is little reduction of caries. This level will depend on the animal model being tested. In one study using gnotobiotic rats, it was as low as 3 per cent sucrose,[56] although this has not been the experience of other investigators (Guggenheim, König: personal communications). In conventional rats the threshhold level has been estimated at 15 per cent sucrose[31] and 25 per cent sucrose,[29] and in conventional hamsters, at 20 per cent sucrose in the diet (Krasse, unpublished findings). This relationship is shown diagrammatically in Figure 3, and may also explain why in some human trials, in which only one food item was varied, no significant differences in caries were found. The frequency of eating dietary sucrose

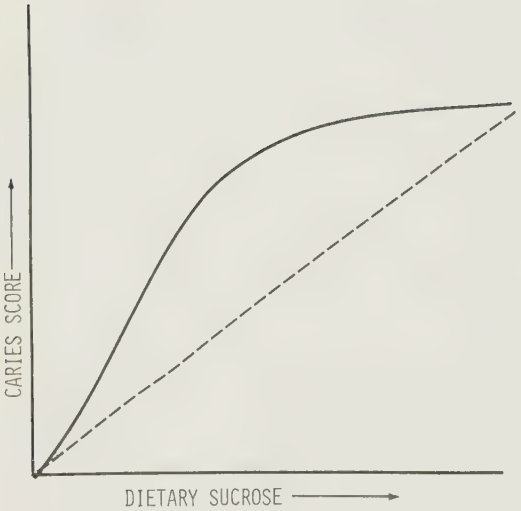


Figure 3. Possible relationship between caries score and dietary sucrose intake. Broken line represents a perfect linear relationship, solid line resembles findings with experimental animals.

would alter the shape of the curve. For example, if sugary foods are eaten only at meal times, the curve would shift to the right and probably not rise as steeply. However, the trend in eating patterns in the United States has been toward more snack servings of sugary foods and less eating of desserts at meals.[50] Under such circumstances, the relationship between dietary sucrose and caries will approximate an S-shaped curve rising steeply even at moderate concentrations of sucrose in the diet.

What is the threshhold level of sugar content above which a food is highly cariogenic and highly acidogenic? The answer requires some value judgement but is supported both by animal studies on cariogenicity and by human studies on the drop in plaque pH. Foods containing 15 to 20 per cent sugar (especially sucrose) or more must be considered potentially cariogenic and unsafe as snack foods. Foods containing 10 to 15 per cent sugar (especially sucrose) are suspect and their use between meals is contraindicated.

CONCLUDING REMARKS

Caries, once developed, cannot be "cured" and therefore the emphasis must of necessity be on prevention. Communal water fluoridation is unquestionably a practical, inexpensive, and highly efficacious means of preventing caries.[64] However, because political support is lacking (not because of controversy in the scientific or health community), only about 60 per cent of the United States population using public water supplies are benefiting from this proven public health measure. But even if all communities were fluoridated, caries would

not be totally eliminated and we would still have to employ other known preventive methods. Oral hygiene is most important in preventing periodontal diseases. However, oral hygiene *per se*, exclusive of therapeutic dentifrices, has had an insignificant effect on caries increments.[33, 77] There are several explanations for this. In part, it is because caries most commonly occur in fissures, which cannot be properly cleaned by any available method. Another important reason is that teeth are usually brushed in the morning and before going to bed but not immediately after eating, when the demineralization of enamel is taking place. Occlusal sealants will, when placed in newly erupted teeth, significantly reduce the occurrence of fissure caries but have no effect on smooth surface lesions.

These are the reasons why dietary modification is so critical in any total dental preventive program. No caries-preventive program is complete unless it includes dietary modification and restriction on the frequency of ingestion of sugary foods.

REFERENCE

1. Andlaw, R. J.: Diet and dental caries — a review. J. Hum. Nutr., *31*:45, 1977.
2. Ashley, F. P., Naylor, M. N., and Emslie, R. D.: Clinical testing of dicalcium phosphate supplemented sweets. Brit. Dent. J. *436*:361, 1974.
3. Bagramian, R. A., Jenny, J., Frazier, P. J., et al.: Diet patterns and dental caries in third grade U.S. children. Comm. Dent. Oral Epidemiol., 2:208, 1974.
4. Bagramian, R. A., and Russell, A. L.: Epidemiological study of dental caries experience and between-meal eating patterns. J. Dent. Res., 52:342, 1973.
5. Barmes, D. E.: WHO's accent on prevention. Scand. J. Dent. Res., *85*:11, 1977.
6. Bibby, B. G.: The cariogenicity of snack foods and confections. J. Amer. Dent. Assoc., *90*:121, 1975.
7. Birkhed, D., and Edwardsson, S.: Acid production from sucrose substitutes in human dental plaque. *In* Guggenheim, B., ed.: Health and Sugar Substitutes. Basel, S. Karger, 1978, p. 211.
8. Boever, J., de, Hertzel, H. C., and Mühlemann, H. R.: The effect of concentrated sucrose solutions on pH of interproximal plaque. Helv. Odontol. Acta., *13*:27, 1969.
9. Boever, J., de, and Mühlemann, H. R.: pH of interproximal plaque with regard to continuous sucrose application. Helv. Odontol. Acta, *13*:97, 1969.
10. Bowen, W. H.: Role of carbohydrates in dental caries. *In* Wei, S.H.Y., ed.: Proceedings of the National Symposium on Dental Nutrition. University of Iowa Press, 1979 (in press).
11. Carlos, J. P., ed.: Prevention and Oral Health, DHEW Publication No. NIH 74-707. Washington, D.C., USGPO, 1974.
12. Carlos, J. P., and Gittelsohn, A. M.: Longitudinal studies of the natural history of caries. II. Arch. Oral Biol., *10*:739, 1965.
13. Cereal Institute: The role of presweetened breakfast cereals in the American diet. Information from Cereal Institute Inc., Chicago, Illinois, 1974.
14. Chung, C. S., Witkop, C. J., and Henry, J. L.: A genetic study of dental caries. Amer. J. Hum. Genet., *16*:231, 1964.
15. Edgar, W. M.: The role of saliva in the control of pH changes in human dental plaque. Caries Res., *10*:241, 1976.
16. Edgar, W. M., Bibby, B. G., Mundorff, S., et al.: Acid production in plaque after eating snacks: modifying factors in foods. J. Amer. Dent. Assoc., *90*:418, 1975.
17. Fehr, F. R. von der, Löe, H., and Theilade, E.: Experimental caries in man. Caries Res. *4*:131, 1970.
18. Finn, S. B., and Jamison, H. C.: The effect of dicalcium phosphate on caries incidence in children: 30 month results. J. Amer. Dent. Assoc., 74:987, 1967.
19. Frostell, G.: A method for evaluation and acid potentialities of foods. Acta Odontol. Scand., *28*:599, 1970.
20. Glass, R. L.: Effects on caries incidence of sugar and stannous chelate in chewing gums. ORCA Abst. No. 15, p. 60, 1978.

21. Glass, R. L., and Fleisch, S.: Diet and dental caries: dental caries incidence in the consumption of ready-to-eat cereals. J. Amer. Dent. Assoc., *88*:807, 1974.
22. Graf, H., and Mühlemann, H. R.: Telemetry of plaque from interdental area. Helv. Odontol. Acta, *10*:94, 1966.
23. Grenby, T. H., and Bull, J. M.: Dental caries in laboratory rats from breakfast cereals and its control by a calcium glycerophosphate additive. Arch. Oral Biol., *23*:675, 1978.
24. Grey, A. S., and Hawk, D. R.: Significance of caries experience in preschool children aged 3-5. J. Can. Dent. Assoc., *33*:87, 1967.
25. Guggenheim, B.: Extracellular polysaccharides and microbial plaque. Int. Dent. J., *20*:657, 1970.
26. Gustafsson, B. E., Quensel, C. E., Lanke, L. S., et al.: The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years. Acta Odontol. Scand., *11*:232, 1954.
27. Hardwick, J. L.: The incidence and distribution of caries throughout the ages in relation to the Englishman's diet. Brit. Dent. J., *108*:9, 1960.
28. Harris, R.: Biology of the children of Hopewood House, Bowral, Australia. IV. Observations of dental caries experience extending over five years (1957-1961). J. Dent. Res., *42*:1387, 1963.
29. Hartles, R. L.: Sucrose and dental caries. *In* Yudkin, J., Edelman, I., and Hough, L., eds.: Sugar. London, Butterworth's, 1971, p. 221.
30. Hayden, E. B.: Breakfast and today's life styles. J. School Health *45*:83, 1975.
31. Hennon, D. K., Stookey, G. K., and Muhler, J. C.: Prevalence and distribution of dental caries in preschool children. J. Amer. Dent. Assoc., *79*:1405, 1969.
32. Hoover, C. I., and Newbrun, E.: Microflora of plaque from patients with hereditary fructose intolerance and normal siblings. J. Dent. Res., *57*: Spec. Iss. A., Abst. No. 555, p. 213, 1978.
33. Horowitz, A. M., Suomi, J. D., Peterson, J. K., et al.: Effect of supervised daily plaque removal by children: results after third and final year. J. Dent. Res., *56*: Spec. Iss. A., p. 85, 1977.
34. Huxley, H. G.: The cariogenicity of dietary sucrose at various levels in two strains of rat under unrestricted and controlled-frequency feeding conditions. Caries Res., *11*:237, 1977.
35. Huxley, H. G.: Caries research using experimental animals: methods and measurements. *In* Bibby, B. G., and Shearn, R. J., eds.: Methods of Caries Prediction. Sp. Supp. Microbiol. Abst. 1978, p. 211.
36. Imfeld, T.: Evaluation of the cariogenicity of confectionery by intra-oral wire telemetry. Helv. Odontol. Acta, *21*:1, 1977.
37. Imfeld, T.: *In vivo* assessment of plaque acid production. A long-term retrospective study. *In* Guggenheim, B., ed.: Health and Sugar Substitutes, Basel, S. Karger, 1978, p. 218.
38. Imfeld, T., Hirsch, R. S., and Mühlemann, H. R.: Telemetric recordings of interdental plaque pH during different meal patterns. Brit. Dent. J., *144*:40, 1978.
39. Imfeld, T., and Mühlemann, H. R.: Evaluation of sugar substitutes in preventive cariology. J. Prev. Dent., *4*:8, 1977.
40. Ishii, T., König, K. G., and Mühlemann, H. R.: The cariogenicity of different between-meal snacks in Osborne-Mendel rats. Helv. Odontol. Acta, *12*:41, 1968.
41. Keyes, P. H.: Present and future measures for dental caries control. J. Amer. Dent. Assoc., *79*:1395, 1969.
42. Krasse, B.: The effect of caries-inducing streptococci in hamsters fed diets with sucrose or glucose. Arch. Oral Biol., *10*:223, 1965.
43. Krasse, B.: The effect of diet on the implantation of caries-inducing streptococci in hamsters. Arch. Oral Biol., *10*:215, 1965.
44. Krasse, B., Edwardsson, S., Svensson, I., et al.: Implantation of caries-inducing streptococci in the human oral cavity. Arch. Oral. Biol., *12*:231, 1967.
45. Kreitzman, S.: Human diet and dental caries. *In* Proc. Workshop on Cariogenicity of Food, Beverages, Confections, and Chewing Gum. Chicago, Illinois, Research Institute American Dental Association Health Foundation, 1977, p. 55.
46. Kreitzman, S. N.: New perspectives on diet and dental caries. J. Prevent. Dent., 5:12, 1978.
47. Larson, R. H., Ambsbaugh, S. M., Navia, J. M., et al.: Collaborative evaluation of a rat caries model in six laboratories. J. Dent. Res., *56*:1007, 1977.
48. Levenson, M. F.: A home oral hygiene device requiring no dexterity. Ohio Dent. J., *38*:14, 1964.
49. Mäkinen, K. K.: The role of sucrose and other sugars in the development of dental caries: a review. Int. Dent. J., 22:363, 1972.
50. Marketing Research Corporation of America: Economic and marketing report on frozen desserts. Prepared by Economic and Marketing Council on Frozen Desserts, 1969, p. 38.

51. Marthaler, T. M.: Epidemiological and clinical dental findings in relation to intake of carbohydrates. Caries Res., *1*:222, 1967.
52. Marthaler, T. M.: Sugar and oral health: epidemiology in humans. *In* Guggenheim, B., ed.: Health and Sugar Substitutes. Basel, S. Karger, 1978, p. 27.
53. Marthaler, T. M., and Froesch, E. R.: Hereditary fructose intolerance — dental status of 8 patients. Brit. Dent. J., *123*:597, 1967.
54. McDonald, J. L., and Stookey, G. K.: Animal studies concerning the cariogenicity of dry breakfast cereals. J. Dent. Res., *56*:1001, 1977.
55. Menczer, L. F.: Hartford's pre-school dental program. J. Amer. Dent. Assoc., *52*:698, 1956.
56. Michalek, S. M., McGhee, J. R., Shiota, T., et al.: Low sucrose levels promote extensive *Streptococcus mutans*-induced caries. Infect. Immuno., *16*:712, 1977.
57. Miller, D. W.: The Micro-organisms of the Human Mouth. König, K., ed. Basel, S. Karger, 1973.
58. Mühlemann, H. R., and Imfeld, T.: Plaque-pH telemetry. *In* Bibby, B. G., and Shern, R. J., eds.: Methods of Caries Prediction. Sp. Supp. Microbiol. Abst., 1978, p. 241.
59. Newbrun, E.: Sucrose, the arch criminal of dental caries. Odont. Rev., *18*:373, 1967.
60. Newbrun, E.: Sugar, sugar substitutes and noncaloric sweetening agents. Int. Dent. J., *23*:328, 1973.
61. Newbrun, E.: Polysaccharide synthesis in plaque. *In* Stiles, H. M., Loesche, W. W., and O'Brien, T. C., eds.: Microbial Aspects of Dental Caries. Sp. Supp. Microbiol. Abst., *3*:649, 1976.
62. Newbrun, E.: Cariology. Baltimore, Maryland, Williams & Wilkins, 1978.
63. Newbrun, E.: Criteria indicative of cariogenicity or non-cariogenicity of foods and beverages. *In* Guggenheim, B., ed.: Health and Sugar Substitutes, Proceedings of the ERGOB Conference, Geneva. Basel, S. Karger, 1978, p. 253.
64. Newbrun, E.: Systemic use of fluorides: assessment of cost/benefit features and practicality. *In* Burt, D. A., ed.: Relative Efficiency of Preventive Procedures in Dental Public Health. Ann Arbor, Michigan, University of Michigan School of Public Health, 1978.
65. Nizel, A. E.: Nutrition in Preventive Dentistry: Science and Practice. Philadelphia, W. B. Saunders, 1972, p. 27.
66. Page, L., and Friend, B.: Level of use of sugars in the United States. *In* Sipple, H. L. and McNutt, K. W., eds.: Sugars in Nutrition. New York, Academic Press, 1974. p. 93.
67. Parfitt, G. J.: The speed of development of the carious cavity. Brit. Dent. J., *100*:204, 1956.
68. Pennington, J. A.: Dietary Nutrient Guide. Westport, Conn., Avi Publishing Co., 1976.
69. Retief, D. H., Cleaton-Jones, P. E., and Walker, A. R. P.: Dental caries and sugar intake in South African pupils of 16 to 17 years in four ethnic groups. Brit. Dent. J., *138*:463, 1975.
70. Rowe, N. H., Anderson, R. H., and Wanninger, L. A.: Effects of ready-to-eat breakfast cereals on dental caries experience in adolescent children: a three-year study. J. Dent. Res., *53*:33, 1974.
71. Rugg-Gunn, A. J., Edgar, W. M., Jenkins, G. N.: The effect of eating some British snacks upon the pH of human dental plaque. Brit. Dent. J., *145*:95, 1978.
72. Schamschula, R. G., Barmes, D. E., Keyes, P. H., et al.: Prevalence and interrelationships of root surface caries in Lufa, Papua, New Guinea. Comm. Dentl. Oral Epidemiol., 2:295, 1974.
73. Scheinin, A.: Influence of the diagnostic level on caries incidence in two controlled clinical trials. ORCA Abst., No. 20. p. 65, 1978.
74. Scheinin, A., and Mäkinen, K. K.: Turku sugar studies. I-XXI. Acta Odontol. Scand., *33*(Suppl. 70), 1975.
75. Scherp, H. W.: Dental caries: prospects for prevention. Science, *73*:1199, 1971.
76. Shannon, I. L.: Brand Name Guide to Sugar. Chicago, Illinois, Nelson-Hall, 1977.
77. Silverstein, S., Gold, S., Heilbron, D., et al.: Effect of supervised deplaquing on dental caries, gingivitis and plaque. J. Dent. Res., *56*(Spec. Iss. A): A85, 1977.
78. Sognnaes, R. F.: Analyses of wartime reduction of dental caries in European children. Amer. J. Dis. Child., *75*:792, 1948.
79. Stadt, Z. M.: Socio-economic status and dental experience of 3911 5-year-old natives of Contra Costa county, California. J. Publ. Hlth. Dent., *27*:2, 1967.
80. Steinberg, A. D., Zimmerman, S. O., and Bramer, M. L.: The Lincoln dental caries study. II. The effect of acidulated carbonated beverages on the incidence of dental caries. J. Amer. Dent. Assoc., *85*:81, 1972.
81. Stephan, R. M.: Changes in the hydrogen ion concentration on tooth surfaces and in carious lesions. J. Amer. Dent. Assoc., *27*:218, 1940.
82. Stephan, R. M.: Effect of different types of human foods on dental health in experimental animals. J. Dent. Res., *45*:1551, 1966.
83. Stoppelaar, J. D. de, Houte, J. van, and Backer Dirks, O.: The effect of carbohydrate

restriction on the presence of *Streptococcus mutans, Streptococcus sanguis* and iodophilic polysaccharide-producing bacteria in human dental plaque. Caries Res., *4*:114, 1970.
84. Takeuchi, M.: Epidemiological study on dental caries in Japanese children before, during and after World War II. Int. Dent. J., *11*:443, 1961.
85. Terhune, J. A., Predicting the readiness of elementary school children to learn an effective dental flossing technique. J. Amer. Dent. Assoc., *86*:1332, 1973.
86. Toverud, G.: Child dental health. Brit. Dent. J., *116*:229, 1964.
87. Walker, A. R. P., and Cleaton-Jones, P. E.: Dental caries and sugar intake. Lancet, 2:765, 1975.
88. Wells, J. E., Copland, J., Carter, W. J., et al.: Oral health survey of 22,550 Kansas City, Missouri, elementary school children, S. Mo. St. Dent. Assoc., *38*:8, 1958.
89. Winter, G. B., Sucrose and cariogenesis. Brit. Dent. J., *124*:407, 1968.
90. Wirthlin, M. R.: The role of preventive dentistry in the Navy. U.S. Navy Med., *69*:22, 1978.
91. Wisan, J. M., Lavelle, M., and Colwell, M. F., Dental survey of Philadelphia pre-school children by income, age, and treatment status. J. Amer. Dent. Assoc., 55:1, 1957.
92. World Health Organization: The Etiology and Prevention of Dental Caries. Report of a WHO scientific group, Technical Report Series No. 494, Geneva, Switzerland, 1972.
93. Wretlind, A. World sugar production and usage in Europe. *In* Sipple, H. L., and McNutt, K. W., eds.: Sugars in Nutrition. New York, Academic Press, 1974, p. 81.
94. Yudkin, J.: Carbohydrate confusion. J. Roy. Soc. Med., *71*:551, 1978.

Dietary Recommendations for the Maintenance of Dental Health

*Bette Caan, M.S.**

When considering dietary recommendations for the maintenance of dental health we must ask outselves the following questions: Is there a special type of nutrition that is unique to the promotion of dental health? Or, stated differently, is nutrition for oral health different from nutrition for the maintenance of overall well-being?

Nutrition for oral health deals with a unique histologic, anatomic, biochemical, and functioning structure. The tooth is the only organ of the body that is metabolically inert. The tooth is acellular.[1] Certain foods are more deleterious to the teeth than others. In the preceding paper Dr. Newbrun states some characteristics that highly cariogenic foods have in common: (1) they are eaten frequently, often between meals; (2) they have the ability to lower the pH of the plaque; (3) they are adhesive or sticky and may be retained in the oral cavity for a long period of time; and (4) they contain sucrose or some other fermentable sugar. He states that foods containing 15 to 20 per cent or more added sugar (especially sucrose) must be considered potentially cariogenic and unsafe as snack foods. Foods containing 10 to 15 per cent added sugar (especially sucrose) are suspect and their use is contraindicated.[2]

The above statements indicate that there is indeed a special type of nutrition that is needed to promote oral health. If, as health practitioners, our only concern is to reduce the number of dental caries, it would be a simple job to make dietary recommendations. All we need do is recommend elimination of those foods that contain over 15 per cent sucrose or, more stringently, those over 10 per cent sucrose (refer to Table 1).

* Nutrition Consultant, Berkeley, California

Table 1. *Sucrose Content (Per Cent) of Selected Foods and Beverages*[8]

Baby Food Desserts	0.5–13.5	
Apple and Cranberries (Heinz)	0.5	
Prunes with Tapioca (Heinz)	0.5	
Plums with Tapioca (Gerber)	13.5	
Breads		Most breads are in the 0.0–0.2% range.
Breakfast Foods	0.0–3.4	
Dry Cereals	1.0–68.0	
Shredded Wheat	1.0	
Cheerios	2.2	
Puffed Wheat	3.5	
Alpen	3.8	
Product 19	4.1	
Special K	4.4	
Grape Nuts	6.6	
Corn Flakes (Kellogg)	7.8	
Total	8.1	
Rice Crispies	10.8	
Raisin Bran	10.6	
40% Bran Flakes (Kellogg)	16.2	
Granola	16.6	
All Bran	20.0	
Bran Buds	30.2	
Sugar Pops	37.8	
Frosted Flakes	44.0	
King Vitaman	58.5	
Sugar Smacks	61.3	
Super Orange Crisp	68.0	
Bars and Powders		
Carnation Breakfast Bars	16.6–31.8	
Carnation Breakfast Powders	17.9–36.4	
General Mills Breakfast Squares	22.6–40.4	
Pillsbury Breakfast Powders	37.5–41.8	
Candies	2.8–95.4	
Red licorice (Switzer)	2.8	Most candies contain over 15% sucrose; most mints and hard candies contain over 60% sucrose.
Milky Way (M & M Mars)	26.8	
Milk Chocolate Kisses (Hershey)	56.7	
Hard candy (Jolly Rancher)	85.0	
Spearmint (Certs)	95.4	
Cheeses	0.0–0.2	
Chewing Gum		
Conventional Gum	36.9–84.7	
Sugarless Gum	0.0	
Cookies	11.0–48.4	
Peanut Butter Wafers (Salerno)	11.0	Most cookies contain over 15% sucrose.
Date Cakes (Mother's)	11.7	
Fig Bars (Mother's)	12.9	

Table 1. *Sucrose Content (Per Cent) of Selected Foods and Beverages* (Continued)

Crackers and Wafers	0.0–32.0	
Honey Graham Crackers	13.9	Most crackers contain less than 10% sucrose.
Cinnamon Treats (Nabisco)	25.0	
Cinnamon Crisp (Keebler)	32.0	
Fruits and Vegetables		
Canned Juices	0.1–8.1	
Fresh Fruits	0.9–6.4	
Vetetables	0.0–5.4	
Infant Formulas	0.0–6.0	
Ice Cream Products	8.8–21.0	
Vanilla ice cream	8.8	
Strawberry ice cream	8.9	
Popsicle	11.8	
Lime sherbet	16.8	
Pineapple sherbet	21.0	
Luncheon Meats	0.0–0.9	
Non-Dairy Creamers	0.0–0.4	
Pickles	0.0–29.1	Most sweet style pickles contain more than 10% sucrose
Snack Foods		
Chips, Pretzels, etc.	0.0–2.1	
Cakes and Pies	4.7–40.0	Most cakes and pies are over 10% sucrose.
Snack Puddings	1.8–15.4	
Strawberry Gel (Hunt)	1.8	Most snack puddings are between 10 and 15% sucrose
Raspberry Gel (Hunt)	3.3	
Orange Gel (Hunt)	7.8	
Soft Drinks		
Regular	1.0–9.8	
Diet Soft Drinks	0.0–0.1	

Unfortunately, our job is not that simple. The answer to the question is not clear cut. Nutrition for oral health may be unique but other dietary considerations that contribute to the patient's general well-being cannot be ignored at the expense of promoting oral health. Dietary recommendations for oral health involve the promotion of foods that are nutritionally sound and whose consumption over long periods of time will maintain oral health as well as optimal overall health.

Table 2. *The Basic Four*

	DAILY	IN MODERATION	NOW AND THEN
GROUP I			
Grains, legumes and nuts	Barley	Nuts	Granola cereal
4 servings/day	Beans	Peanut butter	White bread
1 serving = approximately 1 oz.	Bread and rolls (whole grain)	Refined cereals (with less than 15% sucrose)	
	Bulghur		
	Lentils		
	Oatmeal		
	Pasta		
	Rice		
	Soybeans		
	Tortillas		
	Whole grain cereal (except granola)		
GROUP II			
Fruits and vegetables	All fruits and vegetables except those listed on right	Avocado	French fries
4 servings/day	Unsweetened fruit juices	Unsweetened dried fruit	Olives
1 serving = approximately ½ cup	Unsalted vegetable juices	Fruits canned in syrup	
	Potatoes, white or sweet	Salted vegetable juices	Pickles
		Sweetened fruit juice	
		Vegetables, canned with salt	
GROUP III			
Milk products	Buttermilk	Frozen lowfat yogurt	Ice cream
Children: 3–4 servings or equivalent/day	Farmer or pot cheese	Ice milk	Processed cheeses
	Lowfat cottage cheese	Lowfat yogurt (sweetened)	Whole milk*
Adult: 2 servings/day	Lowfat milk	Partially skimmed milk cheese	Whole milk cheeses*
1 serving = 1 cup liquid	Lowfat yogurt, plain	Regular cottage cheese	Whole milk yogurt*
1½ cups soft cheese	Skim milk		
1 oz. hard cheese			
2 cups ice cream or ice milk			
1 cup yogurt			

GROUP IV Poultry, fish, egg and meat 2 servings day 1 serving = 3–4 oz. cooked	*Poultry* Chicken or turkey *Fish* Flounder Haddock Halibut Perch Pollock Rockfish Shellfish, except shrimp Sole Tuna, water packed *Egg* Egg whites	*Fish* Herring Mackerel Salmon Sardines Shrimp Tuna, oil packed *Red meats* Group beef (very lean) Ham Leg of lamb** Loin of lamb* Plate beef* Round steak* Rump roast* Sirloin roast* Veal* *Egg* Whole egg	*Poultry and fish* Deep fried and breaded fish or poultry *Red meats* Ground beef (regular) Liver Pork Pork: loin Pork: Boston butt Spare ribs Untrimmed meats *Egg* Egg yolk
MISCELLANEOUS	*Fats* None	*Fats* Mayonnaise Salad oils Margarines (vegetable oil)	*Fats* Butter Cream Cream cheese Lard Sour cream
Note: Other foods should not be used freely; the middle column suggests some of the better choices.	*Other foods* None	*Other foods* Fig bar Date cakes Graham crackers Popcorn (small amounts of salt and butter)	*Other foods* Angel food cake Animal crackers Banana bread Ginger bread Ginger snaps Sherbet

*Children age 3 or under should use whole milk products on a daily basis.
*Trim all outside fat.

The *Dietary Goals for the United States*, prepared by the staff of the Select Committee on Nutrition and Human Needs of the United States Senate,[12] are food selection guidelines for the American public. Among the *Dietary Goals* recommendations are a decrease in consumption of refined and processed sugars (a large portion of which is sucrose), a reduction in total calories if overweight, and a reduction of some other dietary components: saturated fats, cholesterol, and sodium. The continuous over-consumption of any of these dietary components may be implicated in causing or aggravating certain disease states.

There has been increasing evidence in the last decade that artificial sweeteners such as saccharin may be carcinogenic[5, 6] and that some food additives such as artificial food colors and flavorings may have certain toxic properties.[1, 4, 11] The lack of fiber in the diet has been associated with cancer of the colon and other intestinal disorders.[2, 3] In light of our present knowledge of the effect of intakes of certain nutrients and foodstuffs on health and disease it is prudent to substitute highly cariogenic foods, and foods high in other potentially harmful dietary components, with foods that are low in sucrose and other sugars, low in saturated fat, low in cholesterol, low in sodium, of low caloric density (number of calories per unit weight of food), high in natural fiber, and low in chemical additives. Foods such as french-fried potatoes, salted buttered popcorn, potato chips, pretzels and sugar-free soft drinks are all low in sucrose but high in at least one of the undesirable nutrients or food components cited above. Their low sugar content makes them relatively harmless to the teeth; however, they contribute little toward fulfilling optimal body nutrient needs and thus are not preferable dietary choices.

Table 2 presents a list of foods that are nutritionally sound as well as dentally acceptable. It is an adaptation of the USDA's Basic Four Food Guide[11] which was devised to translate recommendations into simple food choices that the consumer can understand. The recommended number of servings in each group is the minimum amount thought to be appropriate for maintenance of health. The "Daily" category contains foods that have less than 30 per cent of their calories from fat and are usually low in salt and sugar. The "Now and Then" foods contain either a large amount of total fat (at least 50 per cent), or saturated fat; 15 per cent or more sucrose; or large amounts of sodium. Foods to eat "In Moderation" have medium amounts of total fat and low to moderate amounts of saturated fats or large amounts of total fat that is mostly unsaturated. They also contain no more than 15 per cent sucrose.

It has been stated above that foods eaten as between-meal snacks are more cariogenic than foods eaten at meals. There are at least two factors probably contributing to this. The first is that foods usually eaten as snacks are often high in sucrose and are usually sticky or adhesive to the teeth (e.g., candy, cookies, etc.). The second factor is that when those same foods are eaten along with other foods (which usually occurs at mealtime) the chances of them adhering to the teeth are lessened because of the mechanical cleansing properties of the other foods and

thus their cariogenic potential decreases. Two examples can be cited. One is the case of pre-sweetened cereals. Children often consume pre-sweetened cereals (some with as high as 68 per cent sucrose[8]) as between-meal snacks without milk or other liquids. The ability for the sucrose to remain on the teeth and thus be more cariogenic is greater than if the cereal is eaten with milk (as in a breakfast meal) in which the sucrose dissolves into the liquid.

The use of the nursing bottle as a pacifier either at night or during the day can be one of the major reasons for a distinct pattern of rapid tooth breakdown often recognized early in preschool years. The amount of time during a 24-hour period that a child spends nursing appears to be the major factor contributing to this problem. Sweetened milk, juice, soda, or any available sugar in the nursing bottle appears to be the bacterial substrate necessary for the development of the pattern of tooth breakdown known as nursing bottle mouth syndrome.[8] When eaten under conditions in which swallowing is more frequent, these substances do not present the same dental problems.

The information presented in this paper should not be misconstrued as advocating the abandonment of between-meal snacks; however caution should be used regarding the frequency and type of snack foods chosen. Foods containing high percentages of sucrose with sticky or adhesive qualities in general should be avoided, and especially as between-meal snacks eaten alone. Snack foods do not have any special characteristics except that they are eaten as snacks. The highly processed, high fat, sweetened items that are advertised to the public are not the only snack foods available. Foods eaten traditionally at mealtimes often are excellent between-meal snacks.

At present the job of integrating the available nutrition knowledge into dietary recommendations is a difficult one. Health practitioners must examine the current scientific evidence which is often inconclusive and base their advice on the risks and benefits to their individual patients.

REFERENCES

1. Abrams, B. A., Caan, B., Citrøn, L., et al.: Final Report on Phase II of "A Dietary Challenge Study of Artificial Food Colors in Children 1–7 Years Old with Behavioral Disturbances." Submitted to the FDA, Dec. 15, 1978.
2. Burkitt, D. P.: Epidemiology and etiology. J.A.M.A., *231*:517, 1975.
3. Burkitt, D. P., Walker, A. R. P., and Painter, N. S.: Dietary fiber and disease. J.A.M.A., *229*:1068, 1974.
4. Connors, C. K., Goyette, C. H., Southwick, D. A., et al.: Food additives and hyperkinesis: A controlled double-blind experiment. Pediatrics, *58*:154, 1976.
5. Hausman, P.: Updating the Basic Four. Nutrition Action, January 1979.
6. Howe, G. R., et al.: Artificial sweeteners and human bladder cancer. Lancet, 2:578, 1977.
7. Miller, A. B., and Howe, G. R.: Artificial sweeteners and bladder cancer (letter). Lancet, 2:1221, 1977.
8. Moss, S.: The nursing bottle mouth syndrome. *In* The Food that Stays: An Update on Nutrition, Diet, Sugar and Caries. Medcom, 1633 Broadway, N.Y., N.Y., 1977.
9. Newbrun, E.: Dietary carbohydrates; Their Role in Cariogenicity. Med. Clin. N. Amer., 63, September, 1979.

10. Nizel, A. E.: The practice of nutrition in dental caries prevention and control: Where are we, where should we be going? Unpublished paper, 1975.
11. Page, L., and Phipard, E.: Essentials of an adequate diet, facts for nutrition programs. U.S. Department of Agriculture Home Economics Research Report, No. 3, Washington, D.C., 1957.
12. Senate Select Committee on Nutrition and Human Needs. Dietary Goals for the U.S. Washington, D.C., 2nd ed., 1977.
13. Shannon, I. L.: Brand Name Guide to Sugar. Chicago, Nelson-Hall, Inc., 1977.
14. Vaidya, V. G., and Godbole, N. N.: Mutagenicity studies with four food colours using human leucocyte and mouse micronucleus test systems. Abstract. International Symposium on Environmental Agents and Their Biological Effects. Hyderabad, India, Feb.–Mar., 1978.

Evaluation of Nutritional Status in the Outpatient Setting

*Sheldon Margen, M.D.**

Except for the most superficial questioning, the physician's in-office evaluation of nutritional status is generally cursory at best, if not totally nonexistent. As we increasingly learn the importance of nutrition as a concomitant of various illnesses and the possible contribution of malnutrition *per se* to chronic diseases, it becomes mandatory for the physician to incorporate a more thorough nutritional status evaluation into every physical examination. This is important whether the patient comes in for diagnosis of a specific complaint or for routine preventive health care.

Diagnostic Evaluation

Evaluation of nutritional status is particularly important in diagnosis and treatment because many diseases are associated with decreased appetite and poor nutrition. Thus, the creation of an optimal nutritional environment by modification of diet is almost imperative for effective recovery and treatment.

Preventive Evaluation

Although clear-cut *deficiency* diseases are rather rare, (1) malnutrition may also manifest itself as overnutrition, particularly of energy, which, when combined with decreased energy expenditure, can lead to obesity; (2) many possibly toxic materials are ingested with foods; and (3) there is increasingly suggestive evidence that certain diseases are related to chronic intakes of unsatisfactory diets. There also appears to be a certain individual susceptibility to various types of foods or nutrients, in some cases genetically determined (e.g., hyperlipoproteinemia in the early development of atherosclerosis). In addition, we now know that some stages of normal development and/or certain physiologic conditions are highly sensitive to nutritional insult. Among the obvious are pregnancy, lactation, infancy, childhood, adolescence, and old age. This does not mean, however, that the average adult (with whom we are primarily concerned) should be neglected, because there

*Professor of Public Health Nutrition, University of California, Berkeley, California

is mounting evidence that long-term nutritional insults may lead to illness.

Given the above, it is natural to ask why nutrition has been so neglected in therapeutic and particularly preventive medicine. Among the reasons I would cite the following: (1) a lack of conviction on the part of the physician as to the importance of nutrition in health and disease; (2) the difficulty of recognizing the marginally malnourished; (3) the difficulty of establishing associations between various illnesses and nutritional indiscretions which may take years to develop; and (4) the old precept of one disease/one cause has only recently begun to disappear and be replaced by the knowledge that most diseases have multifactorial influences (if not causes) with nutrition acting as one such factor. This revolution in the approach to illness emphasizes the need for physicians to increase their knowledge of nutrition and incorporate nutritional evaluations into their everyday practices.

In order for a physician to do this, many difficulties must be surmounted, both on the part of the physician and the teaching of nutrition as well. Unfortunately, nutrition has been a seriously neglected portion of medical training. Medical students may have lectures on metabolic pathways, structures of various nutrients and other highly technical aspects of "scientific nutrition," but these are of little help in learning how to evaluate the nutritional status of a patient, define a proper diet, and finally educate the patient on proper eating habits. Many of the dietary modifications that are taught have been expressed in overly general terms so that at times they are almost meaningless. One example of this is the prescription of a 1500 calorie diabetic diet. When physicians prescribe this, they usually mean a 1500 calorie diet which is "standardized" by some group and does not consider the patient's cultural habits or lifestyle. In order to help a patient implement dietary management we must be sensitive to the basics of nutrition and the individual needs or else rely upon professionals who *do* have the needed expertise. One of the most difficult barriers to overcome is a general belief which has pervaded medicine for a long time that nutrition really has no effect. This myth has certainly been exploded as far as hospitalized and chronically ill patients are concerned, and fortunately is gradually changing with respect to the patient who appears healthy and is most often seen in everyday practice.

As with any other area of health and medicine, most physicians *do not* have to know every detail of food and nutrition any more than they have to recall metabolic pathways, physiologic responses, or the techniques of a physical therapist or areas of medical specialization. There are well trained ancillary professionals who *do* have this knowledge and can be of great help when consulted. However, what the physician *must* be able to do is carry out sufficient evaluation to determine whether or not a problem exists which may be primarily or secondarily nutritional. If the problem does or may exist, the physician must know how to confirm the existence of the problem (e.g., what diagnostic tests, if any, should be performed and how to interpret these tests). If a problem is suspected or is diagnosed, the patient should be referred

to a nutritionist for further clarification. However, even to suspect an abnormality, the physician must also have a good general knowledge of what constitutes an optimal diet. This becomes even more complex, for we do not all eat alike and individual diets can be excellent in spite of marked differences owing to cultural and ethnic backgrounds of individual patients.

THE NUTRITIONAL EVALUATION

To understand the process of nutritional evaluation (or the determination of nutritional status as it is called) we must realize that as with any medical problem the clinical manifestation of the disorder is the final step of a process. The nutritional process leading to clinical manifestations is usually diagnosed as follows:

Intervention	*Sequence of Events*
History	Primary dietary lack; excess or imbalance vs Deficiency caused by other disease or malfunction, stress, biologic, toxicologic (drugs, etc.)
	↓
Laboratory analysis	Tissue desaturation (or increase) Biochemical abnormality
	↓
Physical examination	Physical abnormality (deficiency or excess)
	↓
Therapeutic trial	Recovery

History

As in virtually any physical evaluation, the history is frequently the most important component. In order to provide an index of suspected malnutrition the physician must first be alert to the possibility that the patient's medical problem or general long range health status does have nutritional implications (e.g. diabetes, anemias, obesity, hyperlipoproteinemias, cardiovascular disease, etc.) The dietary history can be done either by the physician or by a trained nutritionist. Various techniques that can be used to obtain a dietary history include diet diaries, 24-hour recalls, or food frequencies and patterns. Almost all are fraught with potential errors and must be used and interpreted with caution even by the most skilled.

The most simple tool for the physician is probably the use of a food frequency and pattern questionnaire as well as direct inquiry into psychosocial factors which might limit access to food such as poverty, living conditions, beliefs, food likes, dislikes, availability of transportation, storage facilities, and so forth. There are at least two ways to elicit information about frequency and pattern of food intake which the physician can probably learn quite easily. The first has been developed by the USDA and is based on the four food groups as follows: (1) meat group — consisting primarily of meat, fish, fowl; (2) milk

group — consisting of milk, cheese and milk products; (3) cereal group — consisting of cereal and legumes such as beans, bread, breakfast cereals, cooked cereals; (4) fruit and vegetable group. This grouping is an easy way for people to recall the foods they have eaten and for the physician to obtain a history. Generally it is believed that people should eat in a 2-2-4-4 pattern each day, that is there should be 2 servings from the meat group, 2 from the milk group, 4 from the cereal group, and 4 from the fruit and vegetable group. The assumption is that this will insure consumption of a wide variety of foods. This approach has recently been criticized because it does not take into account certain changes in our diet over time resulting in marked alterations in nutrient distribution (e.g., increased sugar, saturated fats) and the effects of food processing. Further, it does not consider that there may be marked differences between foods in any one group. For example, the composition (and possibly the physiologic function) of the fat in meat (saturated) and fish (unsaturated) are entirely different and the nutritional properties of skim milk may be quite different from those of whole milk with cream present, or ice cream which has larger quantities of added cream and sugar.

In view of rising concern that modifications in our diet may be related to certain chronic diseases, other approaches for obtaining dietary histories have been developed. Among the most promising (but still rather controversial) is the use of the Dietary Goals for the United States prepared by the staff of the Select Committee on Nutrition and Human Needs of the United States Senate.[1] The U.S. Dietary Goals suggest that the following changes should occur in our diets: (1) To avoid overweight, consume only as much energy (calories) as are expended; if overweight, decrease energy intake and increase energy expenditure; (2) Increase the consumption of complex carbohydrates and "naturally occurring" sugars from about 28 per cent of energy intake to about 48 per cent of energy intake; (3) Reduce the consumption of refined and processed sugars by about 45 per cent to account for about 10 per cent of total energy intake; (4) Reduce overall fat consumption from approximately 40 per cent to about 30 per cent of energy intake; (5) Reduce saturated fat consumption to account for about 10 per cent of total energy intake; and balance that with polyunsaturated and monosaturated fats, which should account for about 10 per cent of energy intake each; (6) Reduce cholesterol consumption to about 300 mg a day; (7) Limit the intake of sodium by reducing the intake of salt to about 5 grams a day. In order to better understand how these Dietary Goals compare with what is considered the "ordinary diet," Figure 1 is reproduced from the Dietary Goals. Using this method, the physician would inquire regarding the relative meat, fish and fowl intake, the intake of eggs, butterfat, etc., the type of fat used in cooking and baking, the amount and types of carbohydrates consumed, particularly refined carbohydrates such as white bread, the amount of sugar used, the salt consumption and the use of processed foods, about which we frequently know little in terms of nutrient quality or content. If it appears that the diet is abnormally high in any of these areas and that the intake of fruits, vegetables and

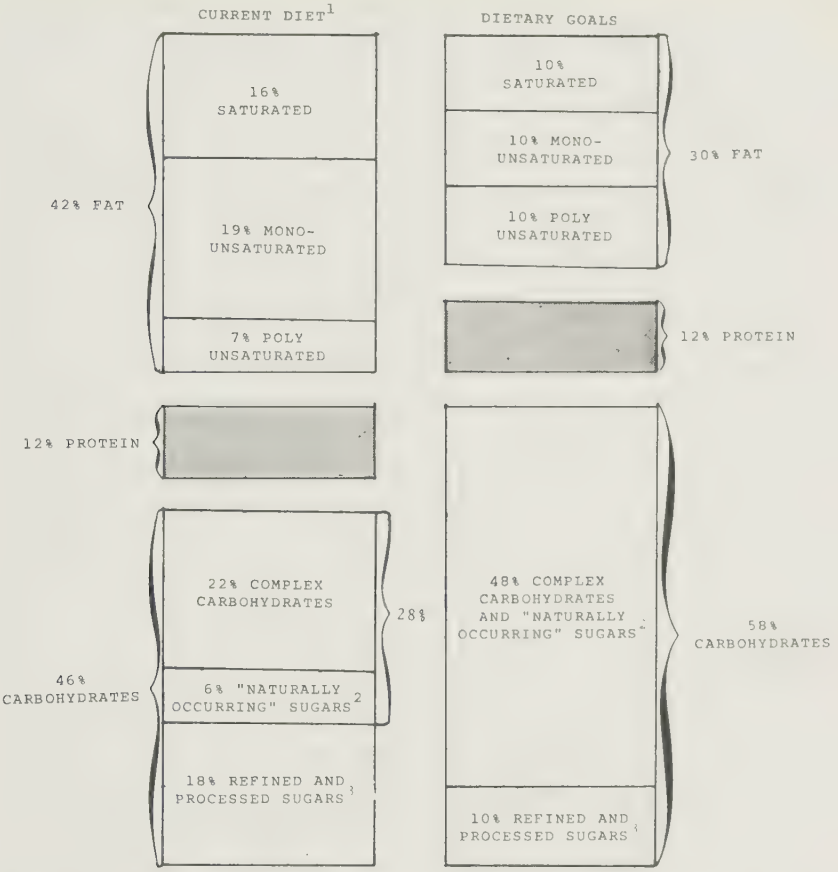


Figure 1. U.S. Dietary Goals.[1] These percentages are based on calories from food and nonalcoholic beverages. Alcohol adds approximately another 210 calories per day to the average diet of drinking-age Americans.

[2]"Naturally occurring": Sugars which are indigenous to a food as opposed to refined (cane and beet) and processed (corn sugar, syrups, molasses and honey) sugars which may be added to a food product.

[3]In many ways alcoholic beverages affect the diet in the same way as refined and other processed sugars. Both add calories (energy) to the total diet but contribute little or no vitamins or minerals.

Sources for current diet: *Changes in Nutrients in the U.S. Diet Caused by Alternations in Food Intake Patterns.* B. Friend. Agricultural Research Service. U.S. Department of Agriculture. 1974. Proportions of saturated versus unsaturated fats based on unpublished Agricultural Research Service data.

whole grains is particularly low, the physician may either give dietary advice to correct the abnormalities (if qualified to do so) or make a referral to a nutritionist or dietitian for a more careful evaluation of nutritional intake. This will allow for a better comparison with both the Dietary Goals and even the Recommended Dietary Allowances (RDA).[2] Note, however, that great caution must be used in interpreting the dietary intake on the basis of the Recommended Dietary Allowances since these were developed for use with populations and a value

for any given nutrient which falls below the RDA does not necessarily indicate a deficiency for an individual patient.

Laboratory Tests

Certain laboratory screening tests are very useful and should be almost routine, particularly among middle-aged males. Among these are hemoglobin, screening for abnormal lipids (such as elevated total cholesterol, low density lipoprotein, cholesterol, total triglycerides, lipoprotein phenotyping, and so forth). Where indicated more specific tests such as iron binding capacity, ferritin, folacin, vitamin B_{12} may obviously be used. Almost all of the vitamins, particularly those which are water soluble, can either be analyzed for their metabolic manifestations to indicate deficiency, or for availability in the body. The same is true of some of the minerals, although with the possible exception of iron, our knowledge in this area is still quite incomplete. Unfortunately few laboratories can carry out many of these more specialized tests, but if necessary they can be ordered from some of the target referral laboratories. The routine use of hair analysis for the diagnosis of trace mineral deficiencies is still in an infantile state and except in the rarest of instances cannot be used to confirm or interpret nutritional abnormalities.

Physical Examination

In the United States the common nutritionally based finding is obesity. In general this can be confirmed by comparing the weight of an individual with certain standards. Although "overweight" does not necessarily indicate obesity, individuals who are overweight because of heavy musculature or special body build can easily be recognized and a simple "pinch test" can help to determine whether there is or is not excess subcutaneous fat. It is rarely necessary to use sophisticated skinfold thickness tests to calculate total body fat. Actual signs of deficiency are generally rare, nonspecific, and may yield only suspicions of nutritional deficiencies. When observed, they must be confirmed with specific laboratory tests to determine whether they are primary or secondary nutritional deficiencies.

This should consist of changing the diet first, either by eliminating or increasing certain nutrients. Adding vitamins or minerals may be a second step when changing dietary patterns is impossible or the change of diet by itself is insufficient to correct deficiencies.

Therapeutic Trials

After the initiation of therapy, many patients claim they feel much better. This must be interpreted with caution since in many instances it is due merely to a placebo effect and not to any actual improvement in function associated with the alteration in nutrition.

In view of the mounting evidence of a relationship between diet and certain degenerative diseases (the so-called "killer diseases") it seems reasonable to recommend that all physicians increase their knowledge of nutrition and be constantly alert to changes in this area.

They should advise all patients to follow a prudent diet, one that is close to that of the U.S. Dietary Goals and to maintain a lifestyle which will promote health (e.g. maintain leanness, activity, lessen stress, avoid smoking, decrease alcohol, etc.) It appears that the old adage, "You are what you eat," may be closer to the truth than we had realized; but perhaps we can now modify this to "You are not only what you eat, but what you eat may cause you to become what you need not have been."

REFERENCES

1. Senate Select Committee on Nutrition and Human Needs. Dietary Goals for the United States 1977.
2. Committee on Dietary Allowances, Food and Nutrition Board, National Research Council. Recommended Dietary Allowances.

Department of Social and Administrative Health Sciences
University of California, Berkeley
School of Public Health
Berkeley, California 94720

Nutritional Assessment of the Hospitalized Patient

George L. Blackburn, M.D., Ph.D., and Paul A. Thornton, Ph.D.***

The importance of correct nutritional status to health maintenance as well as the need for proper nourishment to effect satisfactory progress toward regaining health in the sick and/or traumatized, is now generally recognized by most health care professionals. Thus the questions arise concerning how nutritional status can best be measured and when malnutrition is found, how well the severity of malnutrition can be quantitated. Fortunately, a number of methods have been developed in recent years which, when used collectively, provide a reliable index of the nutritional state, both qualitatively and quantitatively. These developments are timely because recent research has shown that malnutrition among hospitalized patients[1, 6, 9, 29] is far more common than previously realized. It is also evident that many people in the general population are malnourished, if overweight, as only one example, is considered as such. From this the case may be made that nutritional assessment should become a part of medical care on all levels.

The latter suggestion is appropriate because experimental evidence has indicated that the relative nutritional state has a direct influence on the operational level of the immune system and other organ functions related to survival.[22] Clinical observations also support this notion since it is generally noted that infection occurs more often and more severely in the poorly nourished. In turn, the infectious state contributes to a decline in nutritional status;[26] thus a vicious downward cycle can develop between these two factors, with serious con-

*Associate Professor of Surgery, Harvard Medical School; Director, Nutrition Support Service, New England Deaconess Hospital, Boston, Massachusetts

**Research Fellow Harvard Medical School On Leave From Department of Clinical Nutrition, University of Kentucky Medical Center, Lexington, Kentucky

The work upon which this publication is based was performed pursuant to Contract GM-22691-04 awarded by National Institute of General Medicine Sciences, DHEW. Data organization and analysis was performed on the PROPHET system, sponsored by the Chemical/Biological Information Handling Program, National Institutes of Health. This is article 647 from the Cancer Research Institute of the New England Deaconess Hospital.

sequences for the individual unless corrective action is taken. Because of the important relationship between immune competency, which can be estimated by measurement of delayed hypersensitivity to recall skin antigens, and protein and calorie deprivation, a tendency to propose this measure as a criterion of protein-calorie malnutrition exists. This tendency should be avoided. Many mechanisms can account for suppressed recall antigen testing. Most frequent are stress of illness and injury of medical therapy (e.g., chemotherapy, radiotherapy, or major surgery). Sepsis may also produce plasma-inhibiting factors or activate T lymphocyte suppression cells, inhibiting a cell-mediated immune response.

Nutritional assessment requires a profile (index) that includes dietary history, as well as anthropometric, biochemical, and immunological testing. Considerable additional information arises as serial measurements (10 to 14 day intervals) give a dynamic sense of the patient's response to illness and the medical/nutritional therapy. Finally, a logic tree will aid a decision-making process that starts with simple surveillance of all patients and progresses to assessment utilizing appropriately inexpensive common laboratory tests available in every community and most hospital clinical pathology laboratories.

The purpose of this paper is to develop a plan of nutritional assessment for hospitalized patients. It is obvious that not all patients are malnourished and thus full assessment of all is not warranted. Rather, we need to be made aware of preliminary clues that can be used as indicators of the poorly nourished state. The patient's diet and medical histories plus some simple, inexpensive anthropometric measurements (weight, height, triceps, subscapular skinfold thickness and midarm muscle circumference) will usually suffice to alert the examiner to the possibility of malnutrition. At this point, if malnourishment is indicated, the physician is justified in continuing the assessment using more sophisticated methods including biochemical studies of the blood and urine as well as tests for immune competency. Thus, we will discuss the various tools of nutritional assessment, the order of their application, the influence of stress on maintenance of body calorie and protein requirements, and the overall rationale for nutritional assessment in the hospitalized patient.

IDENTIFICATION OF CANDIDATES AND METHOD OF ASSESSMENT

Many health workers tend to think of malnutrition in terms of it being closely associated with "classical" vitamin deficiency syndromes.[10] However, under today's conditions, such deficiencies are rare and although they cannot be forgotten, it is much more probable that protein-calorie malnutrition will be found. Support for this statement are research results[1, 9, 29] which illustrated various degrees of protein-calorie malnutrition in 25 to 50 per cent of the medical and surgical patients that had been hospitalized at least two weeks. Since it is gen-

erally accepted that protein-calorie malnutrition influences the hospital course and has a direct bearing on morbidity and mortality, it follows that one should become familiar with those body changes and clinical conditions that are commonly associated with protein-calorie malnutrition and its development.

An excellent clue of impending protein-calorie malnutrition is a recent weight loss of 10 per cent or more. In clarification, the time element is important. For example, a 10 per cent weight loss in less than 2 weeks, in the absence of accompanying infection, is likely to be a problem of fluid balance more than a reflection of loss of either adipose tissue or lean body mass. On the other hand, a similar weight loss over a 1 to 3 month period would be indicative of loss of both adipose tissue and lean body mass and suggestive of developing protein-calorie malnutrition. The higher the percentage of lean body mass lost, the more severe the protein-calorie malnutrition. This presupposes that the individual had not been following a weight reduction dietary regimen (10 per cent of weight loss occurring from loss of lean body mass). In the absence of the latter, it would be entirely logical to make more assessments. In the interest of time and economics, additional anthropometric techniques would be appropriate.

Particularly needed at this point would be information concerning the physiochemical composition of the weight lost. This is so because the loss of lean body mass is of greater concern both physiologically and pathologically than is an equal loss of adipose tissue. In support of this supposition are the weight loss patterns and consequences seen in starvation alone, compared to starvation associated with illness and injury. Starvation alone does not cause high mortality rates until a 40 per cent weight loss has occurred,[17, 23] while starvation plus illness and/or injury results in high death risks after only a 25 per cent weight loss.[20] This situation exists because the body adjusts to starvation by decreasing the metabolic rate, and secondly the body adaptively conserves lean body mass via greater central nervous system use of ketones in place of glucose, normally generated by gluconeogenic action.[11] In contrast, when non-eating is combined with trauma there is no reduction in the metabolic rate and continuing gluconeogenesis which perpetuates protein catabolism and reduced efficiency of use of dietary protein. The latter appears to be proportional to the severity of the injury[13, 25] and lasts as long as the acute phase of the trauma persists.[5] Thus, it is clear that starvation associated with trauma both accelerates the rate of weight loss and causes a relatively greater loss of lean body mass compared to adipose tissue.

In view of the foregoing, it follows that an analysis of the composition of that weight lost is important. This can be done initially by assessing the remaining fat stores via a skinfold thickness measurement (Fig. 1). In turn, protein stores can be estimated by measuring the arm circumference and calculating the arm muscle circumference by using the following relationship:

$$\text{Arm muscle circumference} = \text{Arm circumference (cm)} - [0.314 \times \text{triceps skinfold (mm)}].$$

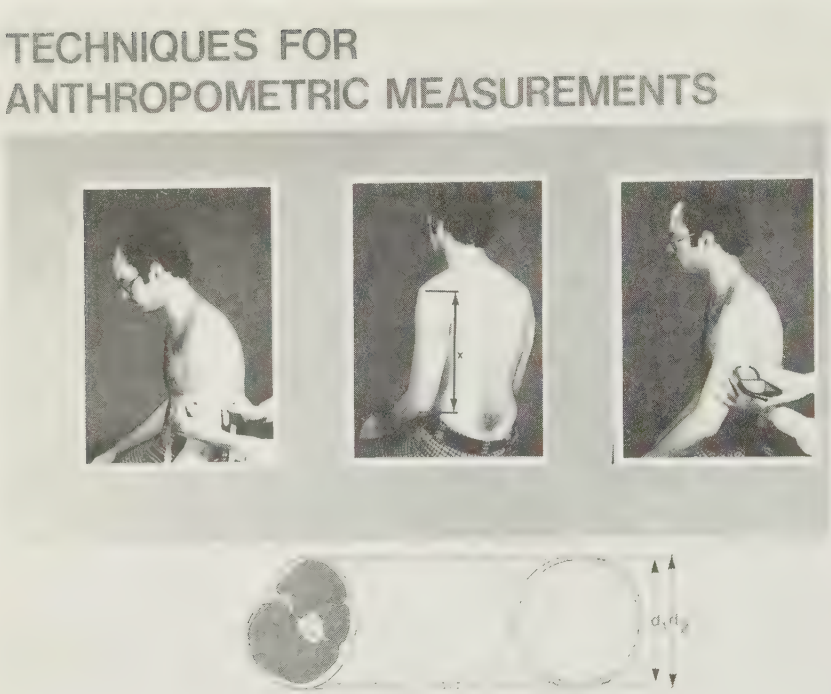


Figure 1. Techniques for anthropometric measurements.

Complete details of both procedures are available.[15] Briefly, the site of measurement for both skinfold and arm circumference is located at the midpoint between the acromial process of the scapula and the olecranon process of the ulna (Fig. 1). For assessing skinfold thickness, at least three separate measurements should be made (the skin pinched and released for each measurement) and the final value taken as an average of the two closest results. Standards for these two measures are charted in Table 1. The actual results obtained can then be compared to these standards and the degree of fat and protein loss estimated. Normally, a score ranging from 60 to 80 per cent is considered moderate malnutrition while anything less than 60 is classified as severe malnutrition.

While both of these methods are subject to error, research evidence has generally indicated their reliability. For example, the triceps site for skinfold was found to be the most predicative among a number of body sites tested in a study involving 22,000 people.[27] Additionally, this area's values were found to be correlated with radiologic evidence[34] and with direct measurements made at surgical operations.[16] Similarly, the method for determining arm muscle circumference, therefore protein stores, can be criticized because it is assumed that the cross-section of the mid-arm muscle compartment is circular and

Table 1. *Adult Standards for Anthropometric Measurements*[*]

	STANDARD	90 PER CENT OF STANDARD	80 PER CENT OF STANDARD	70 PER CENT OF STANDARD	60 PER CENT OF STANDARD
		TRICEPS SKINFOLD (MM)			
					Significant Loss
Male	12.5	11.3	10.0	8.8	7.5
Female	16.5	14.9	13.2	11.6	9.9
		ARM MUSCLE CIRCUMFERENCE (CM)			
			Significant Loss		*Severe Loss*
Male	25.3	22.8	20.2	17.7	15.2
Female	23.2	20.9	18.6	16.2	13.9

[*]Less than 5 per cent of the population have <60 per cent of normal tricep skinfold thickness and this represents significant loss of adipose tissue in need of repair. Skinfold thickness less than 5 mm is representative of no detectable fat tissue in this region.[18] Significant loss of lean body mass begins with an 80 per cent category, 70 per cent being indicative of moderate protein-calorie malnutrition and <60 per cent severe protein-calorie malnutrition.

that the bone is relatively consistent in size. Actually, the mid-upper arm is more elliptical[18] than circular, and while the bone's diameter does remain relatively constant individually, there can be considerable variation among population groups. Nevertheless, this assessment correlates well with the obvious manifestation of protein-calorie malnutrition in that it reflects muscle wastage. Additionally, the site is accessible and the area is usually free of edema, a potential source of error. The value of the two procedures is that they serve to give the quickest and easiest means of obtaining a preliminary estimate of calorie and protein stores. In short, they along with body weight loss, are clues which should serve to alert the examiner to the presence or absence of possible malnutrition.

MORE SENSITIVE TESTS FOR MALNUTRITION

To obtain more definitive evidence, if malnourishment seems probable, one needs to use broader and more sensitive tests. At present, a number of clinical laboratory methods including serum albumin, lymphocyte/total, iron-binding capacity, and creatinine-height index are now so used. These determinations result in a refinement of protein storage values, they provide information concerning visceral protein status, and they permit some predictability of immune function.

Albumin and Transferrin

The plasma proteins are generally reduced as the body loses protein stores. Even though it is usually agreed that the organism's ability

to alter the rate of albumin synthesis is slow (half-life of 16 to 18 days) compared to other plasma proteins, it has been shown that it, as well as transferrin (half-life of 6 to 8 days), provides evidence of the visceral protein status.[2] Morevover, biochemical alterations characteristic of pediatric kwashiorkor occur when albumin levels are below 3.0 gm per 100 ml.[36] Other examples of this relationship include a depression of lymphocytes, anergy, reduced antibody responses to stimulation and diminished lymphocyte transformation to mitogens.[2, 21] Nutrition repletion sufficient to restore serum albumin levels also corrects the parameters just discussed.[2, 21]

Since serum transferrin and albumin levels are correlated,[2] either one or both can be measured as an estimate of visceral protein status with some advantages for use in each case.* For example, transferrin has a shorter half-life and equilibrates more rapidly indicating that it is a more sensitive evidential of visceral secretory protein status than is albumin. This could be a factor in cases where serial measurements are made. Serum transferrin can be derived by first determining the serum total iron-binding capacity (TIBC) and applying the following formula:[15]

$$\text{Serum transferrin} = (0.8 \times \text{TIBC}) - 43$$

In favor of albumin analysis are factors such as its correlation with changes in arm muscle circumference,[5] that it is a reliable indicator of visceral protein activity,[2, 21] and finally, that it is easy and inexpensive to determine. Classification of malnutrition according to degree on the basis of serum albumin and transferrin assessments is shown in Table 2. It is important that the practitioner not administer albumin to change this indicator of malnutrition. Low albumin is not directly involved in the pathogenesis of protein-calorie malnutrition, but merely indicates that dietery intake (primarily protein) and/or nutrient use, via body metabolism is not adequate for optimal protein synthesis. Further albumin infusions used to preserve oncotic pressure and volume expansion of intravascular fluid compartment may invalidate albumin as an index of protein-calorie malnutrition. Transferrin

*These measurements may be altered by organ failure, particularly severe liver disease, severe or acute renal disease and congestive heart failure. They must be interpreted in light of dietary and medical histories as well as other measurements of a complete nutrition assessment index to identify type and magnitude of protein-calorie malnutrition.

Table 2. *Serum Assessments and Malnutrition*

	SERUM ALBUMIN (gm/100 ml)	SERUM TRANSFERRIN (mg/100 ml)
Mild	3.0–3.5	150–175
Moderate	2.1–3.0	100–150
Severe	<2.1	<100

Table 3. *Ideal Urinary Creatinine Values*

MEN*		WOMEN†	
Height (cm)	Ideal Creatinine (mg)	Height (cm)	Ideal Creatinine (mg)
157.5	1288	147.3	830
160.0	1325	149.9	851
162.6	1359	152.4	875
165.1	1386	154.9	900
167.6	1426	157.5	925
170.2	1467	160.0	949
172.7	1513	162.6	977
175.3	1555	165.1	1006
177.8	1596	167.6	1044
180.3	1642	170.2	1076
182.9	1691	172.7	1109
185.4	1739	175.3	1141
188.0	1785	177.8	1174
190.5	1831	180.3	1206
193.0	1891	182.9	1240

*Creatinine coefficient (men) = 23 mg/kg of ideal body weight.
†Creatinine coefficient (women) = 18 mg/kg of ideal body weight.

then becomes more important as an indicator of deficient liver protein synthesis.

Creatinine Height Index (CHI)

This analysis has been used to measure lean body mass or the metabolically active tissue. It has long been believed that urinary creatinine output was related to the weight of the skeletal muscle mass. Further results with adults have shown that the 24-hour creatinine excretion, basal oxygen use, and lean body mass were correlated.[24] The creatinine height index may be defined as the 24 hour urinary creatinine excretion by a given subject divided by the expected 24-hour urinary creatinine excretion by a "normal" male or female of the same height. The "normal" urinary creatinine excretion is calculated as the product of the mean creatinine excretion for males fed a creatine and creatinine-free diet,[31] and the ideal weight for each height according to Metropolitan Life Insurance standards.[12] This value was found to be 23 mg of creatinine per kg of body weight for males,[31] and 18 mg per kg under similar conditions for females.[3]

The measured daily urinary creatinine excretion is compared with the ideal values from Table 3 to the creatinine height index (CHI).[19, 35]

$$\text{CHI} = \frac{\text{Measured Urinary Creatinine}}{\text{Ideal Urinary Creatinine}} \times 100$$

As an example, the expected urinary creatinine excretion for a male of 177.8 cm is 1596 mg per day. If the actual output were 1200

mg, the CHI would be 1200/1596 × 100 or about 75 per cent of normal. This assessment in known malnourished surgical patients[3] indicated that CHI was a more sensitive index of the body's nutritional status than other measurements including weight for height, nitrogen balance, and serum albumin levels. As mentioned earlier, creatinine excretion in healthy individuals correlates well with oxygen use and lean body mass;[21] however, in patients with wasting disease, creatinine excretion drops and is no longer correlated with body weight. Presumably such changes result from a distortion of body composition, especially the loss of body protein. Since height remains essentially unaltered by malnutrition and creatinine excretion, it continues to correlate with body cell mass, and a CHI affords a means of assessing the nutritional status of the metabolically active tissue by allowing a comparison between expected body cell mass for height and actual body cell mass.

In addition to some of the previously mentioned advantages of the creatinine height index as an indicator of nutritional status, it was noted that fluid retention, whether from hyperalimentation or liver disease, did not alter an abnormally low creatinine height index even though body weight was affected.[3] It also remains that adequate visceral protein stores, reflected by serum albumin levels greater than 3.5 gm per 100 ml, could be intact even when creatinine height index indicated a major deficit in skeletal muscle (marasmus-type protein-calorie malnutrition). Thus it is evident that this assessment is the more sensitive method for estimating body protein stores than, for example, arm muscle circumference. The disadvantage of this analysis is that it requires 24 hour urine collections for best results.[35] This can be done easily in a metabolic ward setting, however, this seemingly simple process can be extremely difficult in a free-living population. A minimum of two consecutive 24-hour collections are required to ensure completion of collection. Nevertheless, the effort may be justified if additional analyses of the urine are performed, for example nitrogen excretion.

Nitrogen balance is useful for measuring the degree and direction of change to dietary support efforts. It is also very useful as an adjunct to determining the caloric need of patients. Most forms of stress which result in increased urea nitrogen excretion as related by Kinney,[19] have a commensurate effect on elevation of resting metabolic expenditure. Further, the two factors appear to maintain a positive correlation throughout the course of most injuries and illnesses. Thus, one can not only use urinary nitrogen excretion as a guide to estimating caloric needs as a clinical situation develops but this same technique is fully as useful during the course of recovery. This is a particularly useful tool if the patient is being nourished via the intravenous route.

In summary, the energy stores of any individual can be estimated via anthropometric measurements — body weight and skinfold thickness determinations. Body protein status is initially appraised using body weight data and arm muscle circumference measurements to

calculate the skeletal muscle mass. Additional protein data are realized by analyzing for serum transferrin and/or albumin. These determinations tell us something about visceral protein status which is very important because it can serve as a guide regarding the level of immune competence that exists. Finally, creatinine height index analysis can be used to evaluate the status of the metabolically active tissue. These assessments are characterized by a progressive rate in difficulty regarding assessment and thus costs. However, they are similarly featured by providing progressively more information. Logically it seems that one should start with the most economical means of assessment and proceed onward. The level of assessment would depend on the patient's need and prognosis.

IMMUNE COMPETENCY

Paramount to the whole idea of nutritional assessment is an evaluation of immune status. Cell-mediated immunity is important in the host's defense against infection. Its depression is associated with increased morbidity and mortality from infectious disease in man and has been observed to be especially evident in surgical patients that have become anergic.[33] Depressed cellular immunity and the effect of short-term nutritional repletion to improve this function has been described in hospitalized adults[2, 21] who became malnourished as a result of disease and the semistarvation regimen employed during the course of hospitalization.

Commonly used measures for cellular immunity include skin tests with recall antigens such as candida, streptokinase-streptodornase (SK-SD), and mumps. The recall antigens are given intradermally and the diameter of the resulting induration, if any, is measured 24 and 48 hours later. The most accurate means of measuring the diameter of the induration is reportedly the "ball pen method" which has been described in detail.[33] A skin test is rated "positive" when the diameter of the indurate at the injection site is 5 mm or more. A normal (immunocompetent) responder is positive (~5 mm) to two or more antigens.

MALNUTRITION AND IMMUNE COMPETENCY

	Total Lymphocyte Count	*Skin Test*
Moderate	800–1200	5–10
Severe (Kwashiorkor-like)	<800	<5 mm

A relatively anergic patient (corresponding to moderate kwashiorkor-like, visceral function attribution) may have a response to only one antigen. Failure to elicit a positive response would classify the patient as anergic, which is comparable to a severe kwashiorkor-like syndrome. In both cases, nutritional therapy is indicated.

Immunity is also evaluated by assessing total lymphocyte counts. Generally a value of less than 1000 is of concern. Earlier work[31] indicated that lymphocytes were the key cells involved in forming an in-

duration at the injection site of recall antigens. Very recently, sequential lymphocyte counts increased with improved nutritional status in surviving patients, but decreased in the non-surviving group given similar nutritional treatment.[28]

NUTRITION/METABOLISM PROFILE

The complete nutritional assessment data based on the anthropometric measurements, clinical laboratory findings, and immune competence studies should be accumulated into an index for the most effective use as illustrated in Figures 2 and 3. This is important because individual assessments that exhibit reduction may vary with the classification of deficiency. For example, protein-calorie malnutrition (Fig. 2) was associated with normal albumin, lymphocyte, and transferrin values, but severe depression was exhibited in energy reserves (triceps skin-fold), lean body mass (CHI), and evidence of cellular immunity.

On the other hand, protein deficiency (Fig. 3) was not associated with reduced protein and energy stores although such patients do exhibit severely depressed capacity for visceral protein synthesis and subsequently a lack of immunocompetence. The data clearly illustrates that when initial observations, diet, or medical histories indicate the possibility of malnutrition, a complete assessment should be conducted in order to classify what types of deficiency are present as well as their severity.

The nutritional metabolic profile has proved to be a reliable means

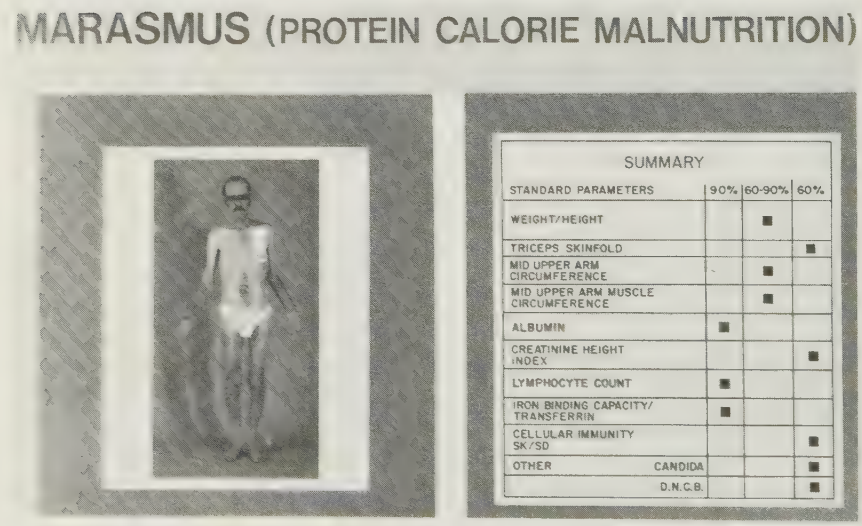


Figure 2. Completed nutritional/metabolic profile of patient with moderate to severe marasmus. (From International Classification of Diseases, 9th Revision, Clinical Modification, Vol. I. Ann Arbor, Michigan, Edward Brothers, Inc.)

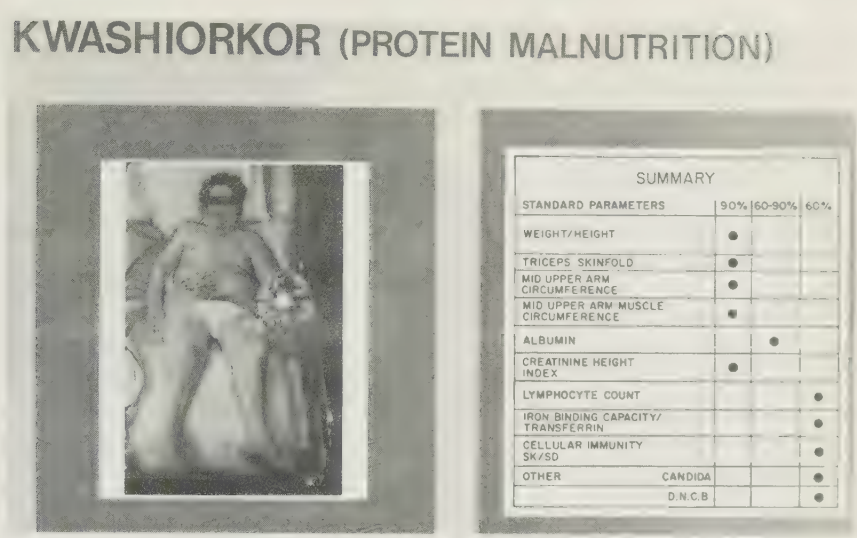


Figure 3. Completed nutritional/metabolic profiles of patient with kwashiorkor-like syndrome. (International Classification of Disease, 9th Revision, Clinical Modification, Vol. I. Ann Arbor, Michigan, Edward Brothers, Inc.)

to illustrate the causes of malnutrition, namely insufficient protein and calories, and can be used as a guide to establish the patient's nutrition therapy program. It is also useful as a tool for monitoring progress of the patient's response to nutritional treatment. Thus, parts of the assessment profile should be repeated at certain intervals (Table 4). With such periodic assessment and charting a continuous record, the patient's initial nutritional status and progress during hospitalization can both be maintained.

The importance of an initial nutritional assessment as well as a continuing schedule as shown (Table 4) in hospitalized patients becomes apparent in view of the following points. (1) Some symptoms of the malnourished state are obvious but others may be subtle. In either case, assessment is indicated to uncover any inconspicuous symptoms and secondly to quantitate those that are apparent. (2) Protein-calorie

Table 4. *Frequency of Clinical Measurements*

ASSESSMENT	INITIAL ASSESSMENT	FOLLOW-UP ASSESSMENT (IF ABNORMAL)
Albumin/Transferrin	On admission	Every 10–14 days with diet
CMI	When indicated	Every 21–30 days support
Anthropometrics	On admission	Every 21–30 days thereafter
Total lymphocyte count	On admission	Weekly
Body weight	On admission	At least 3 times weekly
Creatinine height index	When indicated	Every 21–30 days thereafter

malnutrition is the most common form of acquired immunodeficiency. Impairment of immune function occurs in primary malnutrition which is associated with disease in this society.[1, 26] Some of the latter occurs or is enhanced in hospitalized patients that are given moderate carbohydrate–low protein diets in the presence of a severe catabolic stress. This combination causes a rapid fall in serum albumin levels and depression of cellular immunity; this hypoalbuminemia malnutrition in adults resembles kwashiorkor in this respect.[2] (3) In the marasmus-like situation, the fat and muscle stores provide most of the deficit calories, therefore, secretory protein levels and immune function are less severely affected.[30] Thus, while anthropometric measurements are characteristically depressed, visceral protein status is preserved. This results because there has been an insufficient dietary intake which was uncomplicated by a morbid catabolic response to illness.[4]

SUMMARY

While some symptoms of the malnourished state are obvious, others may be subtle. In either case, assessment is indicated to uncover any inconspicuous symptoms and secondly to quantitate those that are apparent. Such procedures are pertinent because immune competence and other organ systems related to survival are dependent on the adequately nourished state. It is also important to remember that certain vitamin and mineral deficiencies may accompany protein-calorie malnutrition and thus their attention would be especially needed during the repair of this condition. The deficiencies seen most often include vitamins C, A, and D, as well as zinc, copper, and calcium. Furthermore, the refeeding process may also precipitate shortages of potassium, phosphate, and magnesium, unless adequate amounts of these nutrients are included in the diet.

From this and earlier discussed situations, it is suggested that nutritional assessment should be the initial step in nutritional therapy. It should be approached with concern not only for what the collective assessment tools will reveal, but also with consideration for the patient's clinical problem, the current metabolic situation and the projected therapeutic regimen which will be formulated.

REFERENCES

1. Bistrian, B. R., Blackburn, G. L., Hollowell, E., et al.: Protein status of general surgical patients. J.A.M.A., *230*:858–860, 1974.
2. Bistrian, B. R., Blackburn, G. L., Scrimshaw, N. S., et al.: Cellular immunity in semistarved status in hospitalized adults. Amer J. Clin. Nutr., 28:1148–1155, 1975.
3. Bistrian, B. R., Blackburn, G. L., Sherman, M., et al.: Therapeutic index of nutritional depletion in hospitalized patients. Surg. Gynec. Obstet., *141*:512–516, 1975.
4. Bistrian, B. R., Blackburn, G. L., Vitale, V.: Prevalence of malnutrition in general medical patients. J.A.M.A., 235:1567–1570, 1976.
5. Bistrian, B. R., Blackburn, G. L., Vitale, J., et al.: Protein nutrition status of general medical patients. Clin. Res., 22:692A, 1974.
6. Blackburn, G. L.: Nutritional assessment and support during infection. Amer. J. Clin. Nutr., *30*:1493–1497, 1977.

7. Blackburn, G. L., Bistrian, B. R., Maini, B. S., et al.: Nutritional and metabolic assessment of the hospitalized patient. J. Parenteral and Enteral Nutrition, *1*:11–22, 1977.
8. Blackburn, G. L., and O'Keefe, S. J.: Protein sparing therapy during stress and injury. Proc. West. Hemp. Nutr. Cong. V, August 1977. Quebec, P.Q., Canada.
9. Bollet, A. J., and Owens, S. O.: Evaluation of nutritional status of selected hospitalized patients. Amer. J. Clin. Nutr., *26*:931–938, 1973.
10. Butterworth, C. E., and Blackburn, G. L.: Hospital malnutrition and how to assess the nutritional status of a patient. Nutrition Today Vol. 10, No. 2, March/April, 1975.
11. Cahill, G. F., Jr., Herrera, M. G., Morgan, A. P., et al.: Hormone-fuel interrelationships during fasting. J. Clin. Invest., *45*:1751–1769, 1966.
12. Chicago Society of Actuaries. Build and Blood Pressure Study, 1959.
13. Cuthbertson, D. P.: The disturbance of metabolism produced by bony and non-bony injury, with notes on certain abnormal conditions of bone. Biochem. J., *24*:1244–1263, 1930.
14. Eriksson, B., Douglas, H. O., Jr., Homan, P., et al.: Hyperalimentation as an adjunct to the treatment of cancer of the upper gastrointestinal tract. J. Parenteral and Enteral Nutr., *1*:2A, 1977. (Abstract)
15. Fogelson, D., Rienhoff, H. Y., and Blackburn, G. L.: Manuscript in preparation, 1978.
16. Garm, S. M.: Anthropometry in clinical appraisal of nutritional status. Amer. J. Clin. Nutr., *11*:418–432, 1962.
17. Garrow, J. S., Fletcher, J., and Halliday, D.: Body composition in severe infantile malnutrition. J. Clin. Invest., *44*:417–425, 1965.
18. Heymsfield, S. B., Alafson, R. P., Kutner, M. H., et al.: Radiographic method of quantifying protein-calorie malnutrition. Amer. J. Clin. Nutr., in press.
19. Kinney, J. M.: The effect of injury on metabolism. Brit. J. Surg., *54* (Suppl.):435–439, 1967.
20. Kinney, J. M., Duke, J. H., Jr., and Long C. L.: Tissue fuel and weight loss after injury. J. Clin. Pathol., Suppl. *4*:65–72, 1978.
21. Law, D. K., Dudrick, S. J.,and Abdou, N. I.: Immunocompetence of patients with protein-calorie malnutrition. The effects of nutrition repletion. Ann Intern. Med., *79*:545–550, 1973.
22. Law, D. K., Dudrick, S. V., and Abdou, N. I.: The effects of protein calorie malnutrition on immune competence of the surgical patient. Surg. Gynec. Obstet., *139*:257—266, 1974.
23. Lawson, L. J.:Parenteral nutrition in surgery. Brit. J. Surg., 52:795–800, 1965.
24. Miller, A. T., Jr., and Blyth, C. S.: Estimation of lean body mass and body fat from basal oxygen consumption and creatinine excretion. J. Appl. Physiol., 5:73—78, 1952.
25. Moore, F. D., and Ball, M. R.: Metabolic response to surgery. Springfield, Illinois, Charles C Thomas, 1952.
26. Newmann, C. G.: Interaction of malnutrition and infection — a neglected clinical concept. Arch. Intern. Med., *370*:1364–1365, 1977.
27. Pett, L. B., and Ogilvie, G. F.: The Canadian weight-height survey. Human Biol. *28*:177–188, 1956.
28. Pietsch, J. B., Meakins, J. L.,and MacLean, L. D.: The delayed hypersensitivity response: Application in clinical surgery. Surg., *88*–349–355, 1977.
29. Prevost, E. A., and Butterworth, C. E.: Nutritional care of hospitalized patients. Clin. Res. 22:579.
30. Schlesinger, L., and Stekel, A.: Impaired cellular immunity in marasmic infants. Amer. J. Clin. Nutr., 27:615–620, 1974.
31. Scrimshaw, N. S., Hussein, M. A., Murry, E., et al.: Protein requirements of man: variation in obligatory urinary and fecal nitrogen losses in young men. J. Nutr., *102*:1595–1604, 1972.
32. Scrimshaw, N. S., Taylor, L. E., and Gordon, J. E.: Interactions of nutrition and infection (Monograph 57) Geneva. WHO p. 262, 1968.
33. Sokal, V. E.: Measurement of delayed skin-test responses. New Eng. J. Med., 293:501–502, 1975.
34. Tanner, J. M.: The measurement of body fat in man. Prac. Nutr. Soc., *18*:148–155, 1959.
35. Vestergaard, P., and Lauritzen, R.: Constancy of urinary creatinine excretion. Lab. Clin. Med., *51*:211–218, 1958.
36. White, R. G., Coward, W. A., and Lunn, P. G.: Serum-albumin concentration and the onset of Kwashiorkor. Lancet, *1*:63–66, 1973.

Cancer Research Institute
194 Pilgrim Road
Boston, Massachusetts 02215

Nutrition Resources

*Sarah Finkelhor, M.S., M.Ed.**

Do you know where to send your patients for nutrition information? As concern for proper nutrition and the role of prevention have grown, so have the number of trained nutritionists and the number of nutrition oriented programs. Since nutrition is taking on greater importance in clinical practice, health practitioners need to be aware of the variety of nutrition resources available in the community and make them accessible to their patients.

There are five types of nutrition programs widely available throughout the United States. The most pervasive are the federally funded programs established for 'high risk' populations to reduce problems caused by inadequate nutrition. State funded programs provide a variety of clinical and educational services throughout the state. Hospitals and medical centers provide clinical nutrition services as part of comprehensive inpatient and outpatient care. A variety of privately funded programs also provide nutrition resources to a wide consumer audience. Finally, there are community based programs, funded and operated by concerned neighborhood organizations. The following is a brief listing of programs and professional services available in most communities in the United States.

Federal Programs

On the federal level, most nutrition programs are primarily funded by the United States Department of Agriculture (USDA) or the Department of Health, Education, and Welfare (HEW) along with local matching funds or in-kind services. These programs provide a variety of services which may include supplemental food, nutrition counseling, or nutrition education for pregnant women, infants, children, the elderly, as well as general adult populations.

There are four major federal food distribution programs. USDA funds the *Food Stamp Program* which provides food coupons to families or individuals of all ages who meet the income requirements. The coupons are free to the recipient, and they can be used to purchase most domestic food items. Any client living on a very limited budget

*Nutrition Consultant and Doctoral Candidate in the School of Public Health, University of California, Berkeley

Table 1. *Referral Chart for Community Nutrition Resources**

POPULATION GROUP	RISK FACTOR	REFERRAL SOURCE	CONTACT
Pregnant and lactating women	low income	Food Stamps	welfare office
	anemia inadequate weight gain age-related risk factor inadequate diet	WIC Program	city, county or state health department
	adolescent pregnancy inadequate health care	Maternity and Infant Care Project	state health department
	lack of food and nutrition information	EFNEP	Land Grant Universities
		prenatal education	prenatal clinic or private health care team
Infants	low birth weight failure to thrive poor growth patterns	WIC Program	city, county or state health department
	inadequate health care	Children and Youth Project	state health department
Children	poor growth patterns inadequate diet anemia	WIC Program (up to five year of age)	city, county or state health department
	low income	Children and Youth Project (up to 18 years of age)	state health department
		Headstart (preschool)	local community action project
		School Lunch	board of education
		School Breakfast	local community action project

General Adult	Obesity	Weight Watchers International, Inc.	local chapter
		Thin Within	local chapter
		Dieters Workshop	local chapter
		TOPS	local chapter
		Other weight reduction groups	
	Hyperlipidemia	American Heart Association	local chapter
	Cardiovascular disease		
	Hypertension		
	Diabetes	American Diabetes Association	New York, N.Y. (or local chapter)
	low income	Food Stamps	welfare office
	lack of food and nutrition information	EFNEP	Land Grant Universities
	General consumer information[3] for all populations	community nutrition groups	local groups
		community cooperatives	local groups
		American Dietetic Association	Chicago, Illinois 60611
		Center for Science in the Public Interest	Washington, D.C. 20009
		Nutrition Foundation	Washington, D.C. 20006
		Society for Nutrition Education	Berkeley, California 94704
		U.S. Government Printing Office	Washington, D.C. 20402
Elderly	low income	Food Stamps	welfare office
		congregate meal sites	social service agency
	homebound	Meals on Wheels	social service agency
	Diabetes	American Diabetes Association	New York, N.Y. (or local chapter)
	Obesity	weight reduction groups	(see adult section)
	Cardiovascular disease	American Heart Association	local chapter

[3]This is only a partial listing. Programs may vary in different parts of the country.

should be referred to a local welfare office. These are widely distributed throughout the country.

The *Special Supplemental Food Program for Women, Infants, and Children* (WIC), funded by the Department of Agriculture and administered by health agencies, is a supplemental food program that provides health care and nutrition education. This program supplies coupons for specific nutrient-rich foods to pregnant and lactating women, infants, and children up to the age of five, who are at "nutritional risk" and are eligible for free or reduced cost health care. Among the criteria for nutritional risk are anemia, inadequate weight gain during pregnancy, teenage pregnancy, low birth weight, failure to thrive, poor growth patterns, and inadequate dietary patterns. A patient who presents any of these risk factors should be referred to a local WIC Program for assessment of eligibility. All WIC project sites offer the services of a nutritionist. The nutritionist provides individual counseling along with nutrition education classes for the WIC recipients. WIC programs are widely distributed throughout the country in a variety of health care settings.

The School Breakfast and School Lunch Programs, funded by the USDA, provide nutritious meals to children. All meals must conform to nutritional standards that are mandated by law. A child enrolled in both the breakfast and lunch programs will receive two thirds of the daily nutritional needs.[1] These programs were designed to provide children of low income families, through schools, churches, and community centers, with nutritious low cost meals that would help them meet their nutritional requirements. Additionally, nutrition education is now being provided in conjunction with these programs. The School Lunch Program is the most common, however many community groups are trying to get funding for the School Breakfast Program in their regions. If eligible, children should be encouraged to participate in these programs.

The National Nutrition Program for the Elderly authorizes federal funding from the Administration on Aging, for congregate meal sites and home delivered meals. In addition, this program provides a variety of social services and reduces the isolation characteristic of the elderly. The meals are served in local churches and community centers. Nutritionists are involved in monitoring the nutritional quality of the meals and in providing nutrition education to the participants. Many older Americans live on limited budgets. A referral to this type of program can assist in alleviating some of the problems typified by the Older American community.

The Expanded Food and Nutrition Education Program (EFNEP) is funded by the USDA and organized through the Extension Service of Land Grant Universities. Local low income residents are hired and trained as nutrition aides to provide nutrition education to the local population. They conduct home visits to assist in meal planning, budgeting, cooking, and infant feeding, and provide dietary information. They also provide a variety of pamphlets and booklets on various nutrition topics for consumers.

HEW funds a variety of health care programs that include nutrition services. Under the auspices of the comprehensive Maternal and Child Care Act, the *Maternity and Infant Care Project* and the *Child and Youth Project* provide services within a comprehensive multidisciplinary health care setting. "The goal is to provide comprehensive health care, continuity in health management, and supervision of care to low-income and high risk population groups."[1] Because of limited funding, these services are not widely distributed, but they are most often established in ambulatory care clinics.

Headstart, also funded by HEW, is a preschool educational program for low income families. It provides meals for the children and nutrition guidance for the parents. The services of a nutritionist are available at each center. These programs are widely available throughout the country.

State and County Programs

Nutritionists are hired at both state and county levels. State nutritionists, hired by state health departments and state departments of education, are excellent resources for information about various programs throughout the state. County nutritionists, employed by county health departments, usually provide nutrition services in neighborhood clinics such as Well Baby Clinics and Family Health Centers. They frequently work with public health nurses and visiting nurse associations in providing clinical services to a diverse population. Their roles may vary in different locales, however, they are excellent resources and should be consulted for information on appropriate referral sources.

Medical Centers

Medical centers also provide additional nutrition services. Besides the hospital dietary staff that work with the inpatient population, there are nutritionists in ambulatory care settings who provide nutritional assessment and nutritional counseling for patients with special dietary or nutritional requirements. Many Health Maintenance Organizations (HMO), prepaid health plans, also provide nutrition services.

The Private Sector

A wide range of nutrition services operate in the private sector. Since nutrition has developed into a major consumer concern, a variety of nutrition related businesses have appeared. Numerous dietitians and nutritionists have organized private consulting groups that work with physicians and other health care providers to integrate comprehensive nutrition services into patient care. Many obstetricians have hired nutritionists to provide nutritional assessment, monitoring, and counseling of patients throughout pregnancy.

Increasing numbers of physicians are offering nutrition recommendations along with their treatment plans. Individual dietary analyses and dietary recommendations modified to the individual's eating habits can be an extremely valuable component of patient care. Rou-

tine recommendations for dietary supplements have proven to be costly to the patient. It is critical that recommendations be adapted to the individual in order to optimize compliance and effectiveness. For example, if an increase in iron intake is indicated, the patient's dietary sources of iron should be evaluated first and an increased intake of foods high in iron be encouraged, based on sources acceptable to that patient. Then, if necessary, the diet may be supplemented with iron. Supplementation can not compensate for poor eating habits. Nutritionists are trained in techniques of dietary assessment and counseling. Their expertise should be used in the clinical setting. The incorporation of nutrition services in various ambulatory care settings have been shown to improve health maintenance.[4]

Nutrition information can also be obtained from a number of special interest professional and consumer organizations such as the American Academy of Pediatrics, American Diabetes Association, American Dietetic Association, American Heart Association, Center for Science in the Public Interest, The National Foundation/March of Dimes, and the Society for Nutrition Education. These organizations publish and review books, pamphlets, and audiovisual materials on various topics in nutrition and make them available to the public at a nominal cost.

There are also a variety of private weight reduction programs. Some are behavior modification in orientation, with limited risk involved for the client, whereas others use strict dietary intervention, that may be harmful. The long term efficacy of weight reduction programs have not been proven. However they are often times a source of nutrition information, and may be very useful to the participant. Some may be very costly and impractical. They should be critically evaluated for their accuracy and risks as opposed to benefits.

The same cautious approach needs to be applied to the "health food" promoters. All across the country "health food" stores and magazines have become a major source of nutrition information. Many of their claims have raised important issues about the quality of our food supply. As the "prevention" movement grows, consumers need more information so they can adequately assess all dietary and health recommendations. Despite clinical claims, many health food promoters are recommending dietary modifications whose efficacy has never been scientifically proven, although some of these practices have not been determined to be harmful, either. These claims are generally not compatible with scientific research design. In many cases, consumers are functioning as human experiments and should know, as with any intervention program, that the risks and benefits have not been ascertained. Some of these products are harmless but costly. For someone on a limited budget, the benefits of some of these products probably do not outweigh the costs.

Community Programs

Another indicator of the growing prevention movement are the increase in community food cooperatives. These are primarily neighborhood food-buying clubs that purchase bulk orders of fresh and pack-

aged foods from local farmer's markets. These foods are not only cheaper and of higher quality because of their freshness, but they also help to stimulate the local farm economy. Often times, a general exchange of nutritional information occurs between the "co-op" members. This is an ideal organization for individuals and families who live on limited budgets and like to share with others. This may also serve as a low cost alternative to "health food" promotion.

The Individual

The food habits of any individual are an important component of his or her social and cultural identity. In determining nutritional needs it is critical that the individual's own food priorities be considered before making any recommendations or referrals. Nutrition planning can be effective only if the client's values are an integral part of the process. This needs to occur from the beginning. Ask your patients if they are interested in dietary counseling or appropriate food programs. Do they feel they might benefit from a weight reduction program or a nutrition education program? If they express an interest and they demonstrate a need, make the referral and try to reinforce it in later encounters with the patient.

Nutritional changes occur over time with continued adaptation and reinforcement. They are a consequence of a multitude of factors. Food choices have been attributed to individual knowledge and attitudes in and out of home, availability of foods, and community, national, and international public policy decisions.[2] These are all major institutions in our lives, and they change very slowly.

However, we are facing a turning point in our food habits. The quality of our food supply is in question. Scientists and consumers want to know the nutritional impact of the foods we eat. There is concern about the relationship of our diets to disease. Increasing food costs have placed constraints on our food choices. Proper nutrition is a growing concern in our country among both consumers and policy makers. This brief overview shows the diversity of nutrition resources. However many people are not reached by these programs. The nutrition community still needs to respond to growing consumer demands and provide more information to all populations. As a health practitioner, you can play a vital role in providing a supportive environment in which these changes may occur.

REFERENCES

1. Frankle, R. T., and Owen, A. Y.: Nutrition in the Community: The art of delivering services. St. Louis, Missouri, C. V. Mosby Company, 1978.
2. Gifft, H., Washbon, M., and Harrison, G.: Nutrition Behavior, and Change. Englewood Cliffs, New Jersey, Prentice-Hall, 1972.
3. Index of Nutrition Education Materials. Nutrition Foundation, Washington, D.C., 1977.
4. Treacy, L. H.: The nutritionist in a comprehensive health care plan. J. Amer. Dietet. Assoc., 68 (3):253–254, March 1976.

School of Public Health
University of California
Berkeley, California

Index

Note: Page numbers of article titles are in **boldface** type.

Acrodermatitis enteropathica, 1062
Aging, trace elements and, 1063–1065
Albumin, serum, malnutrition and, 1107–1108
Alcohol, effects on nutrients, 987
  heart disease and, 917
Alcoholism, nutrition in, **963–972**
Anemia, in cancer patient, 1014
Anorexia, in cancer patient, 1009
Anorexigenic drugs, 993–994
Antabuse. See *Disulfiram.*
Anthropometric measurements, 1106
Antidepressants, tricyclic, hyperphagic action of, 992–993
Antihistamines, hyperphagic action of, 992
Appetite, drug effects on, 992–995
Ascorbic acid, dietary requirements, in chronic renal disease, 957

Body weight, drugs and, 992–995
Bowel, disease, inflammatory, parenteral nutrition in, 976
  function, fiber and, 1050–1051
Bran. See *Fiber.*

Cachexia, in cancer patient, 1009
Calcium, dietary requirements, RDA, in chronic renal disease, 952–953
Caloric intake, tumor development and, 1027–1028
Cancer. See *Carcinoma.*
Carbohydrate, cariogenicity and, **1069–1086**
  dietary, heart disease and, 917
  metabolism, dietary fat and, 935
    dietary fiber and, 1046–1049
    dietary intake and, 930–933
    in alcoholic, 966
    in diabetes, 929
Carcinogens, nutrients as modifiers of, 1028–1031
Carcinoma, diet and, epidemiologic studies of, 1032–1037
  hormone-dependent, dietary factors and, 1036–1037
  hormone-secreting, 1013
  nutrition and, **1027–1040**
  nutritional problems with, **1009–1025**
  nutritional therapy for, 1021–1022
  parenteral nutrition in, 979
  treatment, nutritional deficiency from, 1015–1020
Cariogenicity, of carbohydrates, **1069–1086**
Celiac syndrome, lymphoma and, 1012
Cellulose, dietary, 1044
Cheese, monoamine oxidase inhibitor reactions with, 989–990
Chemical carcinogens, nutrients and, 1028
Chemical diabetes, 931, 933
Chemotherapy, for cancer, nutritional problems with, 1019–1020
Cholesterol, dietary fiber and, 1049–1050
  heart disease and, 912–916
Coffee, heart disease and, 918
Colon, carcinoma of, diet and, 1034–1036
  dietary fiber and, 1051–1053
Contraceptives, oral, hypovitaminoses and, 1001–1002
Copper, deficiency, parenteral nutrition and, 981, 1057–1058
  metabolism, disorders of, 1062
Coronary heart disease, diet in prevention and management of, **911–925**
Coronary heart disease, risk factors, 912–913
Corticosteroids, appetite stimulating effects, 993
Creatinine height index, 1109–1111

Dental caries, carbohydrates and, **1069–1086**
Dental health, dietary recommendations for, **1087–1094**
Diabetes mellitus, nutritional management, **927–943**

Diarrhea, in cancer patient, 1013
Diet, dental health and, **1087–1094**
in diabetic control, **927–943**
in prevention and management of coronary heart disease, **911–925**
neoplastic development and, epidemiologic studies of, 1032–1037
therapy, in chronic renal disease, **945–962**
tumor development and, **1027–1040**
Dietary Goals, U.S., 1099
Disulfiram (Antabuse) reactions, 991
Diverticular disease, dietary fiber and, 1051
Drug(s), absorption, effects of food on, 985–987
adverse reactions to, food and, 988–990
bioavailability, effects of food on, 985–987
effects on food intake and nutrient absorption, 992
effects on nutrient absorption, 995–997
in mineral depletion, 977–999
interactions with nutrients, 985–1007
intoxication, vitamins for, 1001
vitamins and, 999–1002

ENERGY malnutrition, in chronic renal disease, 946–950
Energy metabolism, in cancer patient, 1010
Enzymes, drug-metabolizing, nutrient inducers of, 1028

FAT, dietary, bowel cancer and, 1035
carbohydrate metabolism and, 935
Fenfluramine (Pondimin), 994
Fiber, carbohydrate and lipid metabolism and, 937
colorectal cancer and, 1036
dietary, **1043–1055**
heart disease and, 917
in diabetic control, 939–940
Fluid and electrolye disturbances, in cancer patient, 1014
Flush reactions, drug-induced, 991
Folacin, dietary requirements, in chronic renal disease, 957
Food, drug interactions and, 988–990, 992–995

GASTRIC carcinoma, diet and, 1033
Gastrointestinal-cutaneous fistula, parenteral nutrition in, 975–976
Genetic disorders, of trace element metabolism, 1061–1062
Giordano effect, 978
Glucocorticoids, appetite-stimulating effects, 993
Glucose, dietary fiber and, 1046–1049

HEART disease, coronary, diet in prevention and management, **911–925**
Hepatolenticular degeneration, 1061
Hospital patient, nutritional assessment of, 1103–1115
Hyperalimentation, **973–983**
Hyperglycemia, with parenteral nutrition, 980
Hyperlipidemia, dietary treatment for, 918–920
Hyperphagic drugs, 992–993
Hypertensive reactions, monoamine oxidase inhibitors and, 989–990
Hypoglycemic reactions, alcohol-induced, 991
Hypopharynx, cancer of, 1033
Hypovitaminoses, with oral contraceptives, 1001–1002

IMMUNE system, nutritional status and, 1031–1032
Immunocompetence, nutritional evaluation for, 1111–1112
Inflammatory bowel disease, parenteral nutrition in, 976
Intestines, mucosal abnormalities, carcinoma and, 1012
Intoxication, drug, vitamins for, 1001
Irritable bowel syndrome, dietary fiber and, 1051
Isocarboxazid (Marplan), adverse reactions to, 989

KIDNEY, disease, nutritional management in, **945–962**
Kidney, failure, parenteral nutrition in, 977–979
Kwashiorkor, 1113

LIGNIN, 1044
Lipid(s), dietary fiber and, 1049–1050
metabolism, dietary carbohydrate and, 933–935
in alcoholic, 966
in obesity, 930
Lipoprotein, metabolism, dietary fat and, 935
Liver, carcinoma of, diet and, 1037
failure, parenteral nutrition in, 978
in alcoholism, 966
Lymphoma, celiac syndrome and, 1012

MALABSORPTION, drug-induced, 997–999
in cancer patient, 1012–1013
Malnutrition, in alcoholism, **963–972**
in chronic renal disease, **945–962**
tests for, **1103–1115**
Marasmus, 1112
Marplan. See *Isocarboxazid.*
Menkes kinky hair syndrome, 1061
Metabolic disorders, genetic, of trace elements, 1061–1062

Mineral, depletion, drugs and, 997–999
Monoamine oxidase inhibitors, food reactions with, 989–991

NARDIL. See *Phenelzine.*
Neurologic disorders, alcohol-related, 967–969
Nitrogen, metabolism, disturbances, parenteral nutrition in, 977–979
Nutrient(s), as modifiers of carcinogens, 1028–1031
  deficiencies, with parenteral nutrition, 980–981
  effect of alcohol on, 964–967, 987
  interactions with drugs, **985–1007**
  recommended dietary allowances, in renal disease, **945–962**
Nutrition, dental health and, **1087–1094**
  in alcoholism, **963–972**
  in cancer patients, **1009–1025**
  parenteral, total, **973–983**
  patient education resources for, 1117–1123
  therapy, for cancer patient, 1021–1022
    in renal disease, **945–962**
  trace elements in, **1057–1068**
  tumor development and, **1027–1040**
Nutritional status evaluation, inpatient, **1103–1115**
  outpatient, **1095–1101**

OBESITY, diabetes and, 928–930, 937–940
  heart disease and, 917
Oral contraceptives, hypovitaminoses and, 1001–1002
Oropharyngeal carcinoma, 1033

PANCREAS, insufficiency, in alcoholic, 965
Pancreatitis, parenteral nutrition in, 976
Parenteral nutrition, metabolic complications, 980–981
  total, **973–983**
  trace elements in, 1057–1062
Parnate. See *Trancylpromine.*
Phenelzine (Nardil), adverse reactions to, 989
Phosphorus, dietary requirements, in chronic renal disease, 952–953
Phytic acid, 1045
Plummer-Vinson syndrome, 1033
Pondimin. See *Fenfluramine.*
Potassium, dietary requirements, in chronic renal disease, 955
Protein, dietary requirements, in renal disease, 951–952
Protein(s), metabolism, in alcoholic, 966
  plasma, in evaluation of nutritional status, 1107–1108
Protein-calorie malnutrition, 1112
Psychotropic drugs, hyperphagic action of, 992
Pyridoxine, dietary requirements, in renal disease, 957

RADIATION therapy, nutritional problems with, 1015–1017
Recommended Dietary Allowances, in chronic renal disease, 950–959
Rectal cancer, diet and, 1034–1036
Renal disease, chronic, nutritional management of, **945–962**
Renal failure, parenteral nutrition in, 977–978

SEPSIS, complicating TPN, 980
  parenteral nutrition in, 978
Sodium chloride, dietary requirements, in chronic renal disease, 953–954
Stomach, alcohol and, 964
  cancer, diet and, 1033

TOOTH decay, carbohydrates and, 1069–1086
Trace elements, dietary requirements, in renal disease, 958
  heart disease and, 917
  in human nutrition, **1057–1068**
Trancylpromine (Parnate), adverse reactions to, 989
Transferrin, malnutrition and, 1107–1108
Tricyclic antidepressants, hyperphagic action of, 992–993
Triglycerides, heart disease and, 913
Tumor(s), development, nutrition and, **1027–1040**
Tyramine reactions, 989–990

UREMIA, nutritional therapy in, **945–962**

VITAMIN(S), deficiency, in cancer patient, 1014
  dietary requirements, in chronic renal disease, 955
  drug interactions with, 999–1002
  for drug intoxications, 1001
Vitamin A, carcinogens and, 1030
Vitamin B_6, dietary requirements, in renal disease, 957

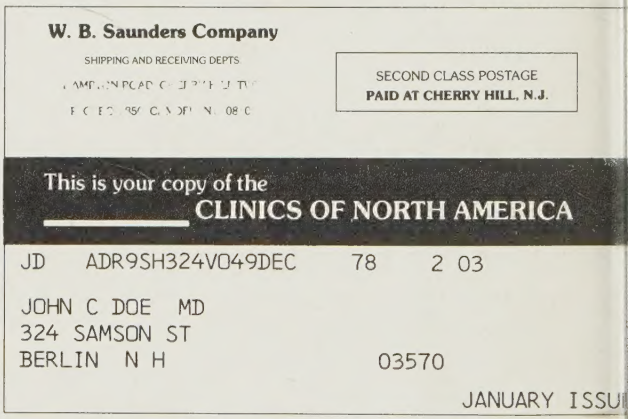
WILSON'S disease, 1061

ZINC, deficiency, parenteral nutrition and, 1057–1058, 1059
  dietary requirements, in renal disease, 958

Changing Your Address?

Make sure your subscription changes too! When you notify us of your new address, you can help make our job easier by including an exact copy of your Clinics label number with your old address (see illustration below). This number identifies you to our computer system and will speed the processing of your address change. Please be sure this label number accompanies your old address and your corrected address—you can send an old Clinics label with your number on it or just copy it exactly and send it to the address listed below.

We appreciate your help in our attempt to give you continuous coverage. Thank you.


W. B. Saunders Company
SHIPPING AND RECEIVING DEPTS
SECOND CLASS POSTAGE
PAID AT CHERRY HILL, N.J.
This is your copy of the
CLINICS OF NORTH AMERICA
JD ADR9SH324V049DEC 78 2 03
JOHN C DOE MD
324 SAMSON ST
BERLIN N H 03570
JANUARY ISSU

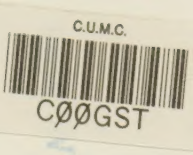
Your Clinics Label Number

Copy it exactly or send your label along with your new address to:
W. B. Saunders Company, Dept. C.A.C.,
West Washington Square, Philadelphia, PA 19105.

If you subscribe to more than one Clinic, please include your Clinics label number (or the entire mailing label) for each subscription.

Please allow four to six weeks for delivery of new subscriptions and for processing address changes.

THIS VOLUME MAY CIRCULATE FOR 1 WEEK
Renewals May Be Made In Person Or By Phone
x 5300; from outside 472-5300



DATE DUE	DATE RETURNED
AUG 19 1980	AUG 1 9 1980
AUG 27 1980	SEP 4 1980
MAY 29 1981	MAY 18 1981
JUL 30 1982	JUL 28 1982
99622	

WEEK SERIAL

C.U.M.C.
CØØGST